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HERITABLE DISORDERS OF CONNECTIVE TISSUE

I. The Clinical Behavior of Hereditary Syndromes

Victor A. McKusick, M.D.

Baltimore, Md.

From the Department of Medicine, The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital

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INTRODUCTION

BECAUSE of the light they shed on normal mechanisms, many of the inherited ailments of man have importance far out of proportion to their numerical significance. Such is the case, at least potentially, with the hereditary disorders of connective tissue, the subject of these studies. This consideration, together with the increasing recognition of internal medical ramifications of these diseases, prompted this survey.

To be discussed are generalized hereditary disorders of connective tissue. Many local hereditary malformations and anomalies can be construed as heritable disorders of connective tissue. These will not be discussed, but rather attention will be concentrated on those heritable diseases which represent abnormality of a single element or biochemical mechanism of connective tissue wherever it is found throughout the body. These include the Marfan syndrome, the Ehlers-

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TABLE I. HERITABLE DISORDERS OF CONNECTIVE TISSUE IN MAN. A SYNOPSIS OF SYMPTOMS

DISORDERS	SKIN	JOINTS	EYE	BONE	BLOOD VESSELS	FASCIA	FUNDAMENTAL DEFECT
Ehlers-Danlos syndrome	Fragility; hyperelasticity	Hyperextensible	Ectopia lentis; microhemorrhages of retina		Dissecting aneurysm (?)	Eventration of diaphragm, hernia	Dystrophy of collagen? Overdevelopment of elastic fibers?
Pseudoxanthoma elasticum	Dystrophy in wear-and-tear areas		Brück's membrane, crazing of: angioid streaks	Paget's disease	Peripheral arteries, medial sclerosis of: hemorrhage		Dystrophy of collagen?
Osteogenesis imperfecta	Thin; abnormal scar formation	Hyperextensible	Sclera, thinning of: blue sclerotics	Brittle bones; otosclerosis (deafness)		Hernia	Maturation of collagen?
Marfan's syndrome		Hyperextensible	Suspensory ligament of lens: ectopia lentis	Excessive length of long bones: dolichostenomelia (long, thin extremities)	Aortic media: aneurysm	Hernia	Defect of elastic tissue?
Hurler's syndrome	Roughening	Limitation of mobility	Clouding of cornea	Dwarfism; dysostosis multiplex	Histologic infiltration	Hernia	Qualitative and/or quantitative abnormality of mucopolysaccharide formation?

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Danlos syndrome, osteogenesis imperfecta, the Hurler syndrome, and pseudoxanthoma elasticum. On the basis of the information available, the nature of certain conditions—Paget's disease of bone, the Brailsford-Morquio syndrome, the Werner syndrome, calcinosis universalis, achondroplasia (chondrodystrophia fetalis), fibrositis (myositis) ossificans progressiva, familial systemic amyloidosis, and others—as possible generalized heritable disorders of connective tissue can only be speculated.

Heritable disorders of connective tissue will be discussed in the following order and under the following headings*:

I. The Clinical Behavior of Hereditary Syndromes.
II. The Biology of Normal Connective Tissue.
III. The Marfan Syndrome.
IV. The Ehlers-Danlos Syndrome.
V. Osteogenesis Imperfecta.
VI. Pseudoxanthoma Elasticum.
VII. The Hurler Syndrome.
VIII. Concluding Comments.

In Table I is presented the connective tissue areas in which clinically evident abnormalities occur in five of these syndromes. The underscored items indicate the predominant manifestations in the case of each. Overlap of manifestations is particularly noteworthy.

Certain features of the behavior of the hereditary syndromes discussed here are common to entities involving other tissues which share enzymatic mechanisms. The hereditary syndromes of connective tissue serve particularly well in demonstrating these features.

As stated above, the several disorders which will be discussed later are *generalized* abnormalities of connective tissue, although predominant presenting manifestations are likely to bring individual cases to the attention of specialists such as dermatologists, ophthalmologists, and orthopedists. Many students of hereditary disease syndromes were in the past preoccupied with germ layers. They were content if all components of a syndrome could be related to a single germ layer and were much perplexed when certain manifestations deviated from the single germ layer hypothesis. When it is appreciated that the abnormality involves one element of connective tissue wherever it is found, no perplexity is occasioned by the occurrence, for example, of ocular involvement in Marfan's syndrome, the other manifestations of which are clearly mesodermal in origin.

Some of the abnormalities resulting from these connective tissue disorders are not congenital malformations in the usual sense but have the nature of *abiotrophies*, the term suggested by Gowers[1] for neurologic disorders in which a tissue is capable of function for only a limited time because of an innate constitutional weakness. For instance, in pseudoxanthoma elasticum the characteristic skin changes are rarely discernible before the latter part of the second

*This series will appear in several successive issues of this JOURNAL. Since the articles are to be published in book form following completion of the series, reprints of individual articles will not be available.—EDITOR.

decade. Furthermore, wear and tear determine predominant localization of the skin lesions in the areas of flexion, of exposure to weather, of irritation by garments, and so on.

The complex clinical syndromes resulting from these disorders of connective tissue are in each instance the result of a *single* mutant *gene*, the action of which has wide repercussions because of its control of some basic biochemical process. The alternative possibility is that of gene linkage, i.e., that the major individual manifestations of a given syndrome are determined by separate genes located in close proximity on the same chromosome. The arguments for a single gene basis of these complex syndromes are as follows:

1. It is unlikely, although possible, that several genes would undergo mutation simultaneously to reproduce these syndromes again and again with such exactitude.

2. "Crossing-over" tends to separate linked characteristics so that in the course of a few generations there is no longer any particular association in a given individual. It is true that for closely neighboring genes the rate of "crossing-over" is so low that the relatively few human generations available to study may, in any one kinship, be inadequate to demonstrate separation of the components of a given syndrome. However, in the population at large, the situation is as stated by Snyder[2]:

> The occurrence of genetic linkage between the genes for two traits does not change the association for these traits in the population from what it would be if they were not linked. Stated conversely, a correlation between two traits in a free-breeding population does not indicate genetic linkage between the genes for these traits.

3. The most telling argument for a single-gene mechanism lies in the possibility of relating all manifestations of these multifaceted syndromes to a single fundamental defect. For example, in osteogenesis imperfecta, the manifestations in the skin, sclera, and bone can be related to a single defect, which may concern the maturation of collagen.[3] If it is possible to construct a convincing "pedigree of causes" relating all clinical manifestations of the syndrome to the basic defect in a descendant fashion, additional strong evidence for the single gene basis of the syndrome has been provided. Gruneberg[4] has constructed such a "pedigree of causes" for certain complex single gene syndromes of the mouse.

4. In both the mouse and the fruit fly there occur syndromes which have as diverse components as any which occur in man and which by more rigorous genetic tests than are possible in man appear to result from a single gene.[5]

"Pleiotropic" is the term customarily applied to these single genes which are responsible for complex syndromes. The implication is that one gene has several actions. It is likely that in fact the gene has but one action and that the apparent multiplicity of its effects is merely the result of the involvement in several processes of the single biochemical step which is controlled by the gene in question. In the strict sense, then, it may be that no gene is truly pleiotropic.

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One occasionally hears statements such as, "That is one of these congenital-familial affairs with which anything can occur." It should not be necessary to emphasize the direct corollary of the single gene proposition: the clinical picture in each of these syndromes is as clear-cut and specific (with, of course, the clinical variability discussed below) as the clinical picture produced by a pathogenic microorganism. In many respects, hereditary disease differs from infectious disease only in that the etiologic agent is a mutant gene operating from within rather than a bacterium invading from without. The virologists have rather long been aware of the basic analogies between their field and that of the geneticist.[6] It is true that in the present state of our ignorance, it is impossible, in the case of some syndromes, to relate all components to a unitary biochemical anomaly. For example, in the syndrome of polyposis of the small intestine and melanin spots of the buccal mucosa, lips, and digits,[7] there is no obvious common denominator. Even in such a situation, however, the other arguments listed above make a single gene mechanism likely.

Wide *variability* in the clinical severity of the manifestations of these syndromes is the rule. This variability is demonstrated particularly dramatically by the syndrome of osteogenesis imperfecta (see later). By the geneticist the clinician's "degree of severity" is referred to as "expressivity." Penetrance, on the other hand, is an all-or-none affair. There will be fundamentally affected individuals in whom the manifestations are so mild that they do not deviate sufficiently from certain ones of the normal group to permit recognition as abnormal. These cases, the cases of incomplete penetrance, of *forme fruste*, correspond to the subclinical cases of infectious diseases. The familiar bell-shaped Gaussian curve probably accurately describes the distribution of cases as to severity (expressivity) (Fig. 1). The three vertical lines of the diagram indicate threshold of penetrance. These lines cross the distribution curve on the side constituted by cases of lesser grades of severity. At this end also the curve is overlapped by the normal distribution curve. The majority of recognizable cases are of intermediate severity; there are some very severe cases and some very mild ones. Those affected individuals in the zone of overlap have mild manifestations which, because of their occurrence as "normal variations" in a small proportion of the normal population, cannot be recognized as abnormal when the individual is studied. For the student of the individual, then, the threshold of penetrance is at the point of overlap of the two curves. A certain number of additional cases can be recognized by the student of the total genetic and clinical picture, by one who investigates the entire family in detail. (There are risks, of course, that some unaffected individuals will be incorrectly classified as affected.) It seems probable that when the basic defect in each of these syndromes is known and when a specific method for demonstrating the defect becomes available, all cases of each syndrome will be identifiable. At this point the threshold of penetrance will be moved back to the limit; and penetrance, an artificial concept at the best, will no longer have significance for these syndromes.

This wide variability in clinical expression is one basis for the phenomenon of "skipped generations" in these syndromes.

The variability in severity of manifestations is both interfamilial and intrafamilial. Interfamilial variability is greater, as a rule, than intrafamilial variability. Assuming that the basic biochemical defect is the same in all instances of a given syndrome, then the basis of variability must be sought in the rest of the genetic make-up of the individual. By and large the factors responsible for this variability are obscure. Occasionally, however, the influence of the genetic milieu on the expression of the mutant gene can be appreciated. For example, the characteristic skeletal changes of Marfan's syndrome tend to be partially submerged when the mutation occurs in pyknic stock; contrariwise, the skeletal changes may be particularly striking when the syndrome occurs in normally asthenic (dolichomorphic) stock.

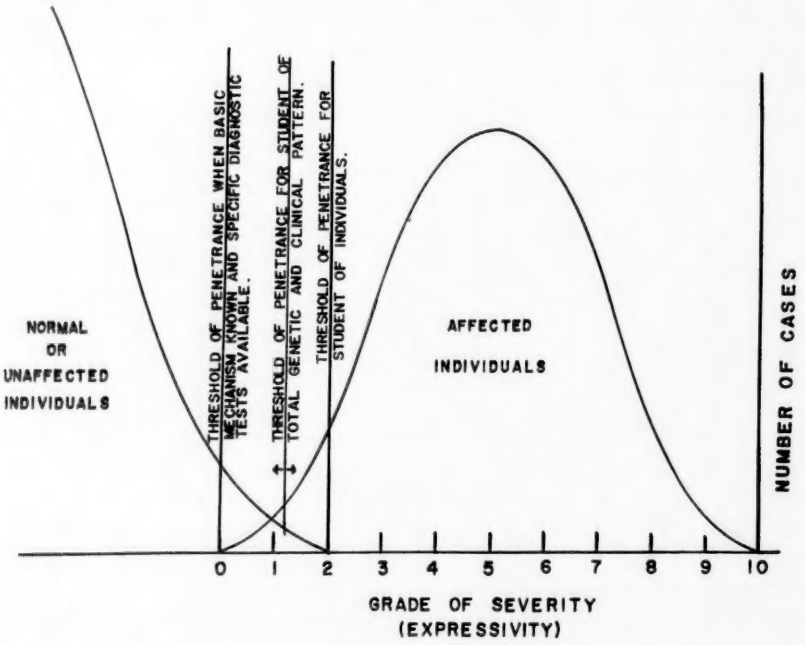
NORMAL
OR
UNAFFECTED
INDIVIDUALS
THRESHOLD OF PENETRANCE WHEN BASIC MECHANISM KNOWN AND SPECIFIC DIAGNOSTIC TESTS AVAILABLE.
THRESHOLD OF PENETRANCE FOR STUDENT OF TOTAL GENETIC AND CLINICAL PATTERN.
THRESHOLD OF PENETRANCE FOR STUDENT OF INDIVIDUALS.
AFFECTED
INDIVIDUALS
NUMBER OF CASES
0 1 2 3 4 5 6 7 8 9 10
GRADE OF SEVERITY
(EXPRESSIVITY)

Fig. 1.—The interrelationship of penetrance and expressivity in hereditary syndromes. (See text.) (Inspired by Dr. H. Bentley Glass.)

The important influence of the genetic milieu is demonstrated by the fact that less variability of expression occurs within a family than does between members of different families. Furthermore, identical twins, identical in respect to their entire gene constitution as well as the mutant gene, usually show onset of symptoms at the same age and show manifestations of the same type and clinical severity.

The analogy between genetic and infectious disease has pertinence also in connection with the clinical variability of hereditary syndromes. As in infectious disease, host factors and host-parasite relationships are of great im-

portance, the "parasite" in the case of genetic disease being the mutant gene, and the host factors mainly the genetic milieu in which mutant gene is operating.

It is a generalization with genetic disorders that wider variability occurs with "dominant" disorders than with "recessive" ones. The suggestion has been made[8] that natural selection tends to choose those genotypes in combination with which the deleterious mutant gene has less devastating effects. The result may be that in time the injurious effects become suppressed in the heterozygote and expressed only in the homozygote. When an hereditary disease has progressed to this stage in its biologic evolution, the disease trait will then display the genetic behavior termed "recessive."

The four disorders other than Hurler's syndrome which will be reviewed in detail display a *dominant* pattern of inheritance. Two features frequently displayed by recessive disease traits are not evident in these four syndromes: (1) a relatively high incidence of consanguinity in the group of parents of affected individuals; and (2) the occurrence of multiple cases in one sibship without involvement of other near relatives (a feature which often led recessive traits to be referred to as "familial"). Experience with other syndromes such as retinitis pigmentosa and Friedreich's ataxia[9] indicate that although the fundamental defect appears to be identical in the several instances (i.e., the "phenotype" is identical) the mode of inheritance may be "dominant" in one pedigree, "recessive" in another. This and the theoretically unstable, evolutionary state of dominance makes it necessary to scrutinize each pedigree individually.

Although the overwhelming majority of the pedigrees of Marfan's syndrome demonstrate a pattern consistent with a dominant mode of inheritance, in rare instances (see later) the inheritance may be recessive. It should not be necessary to point out that whether a disease is transmitted as a dominant or a recessive has no predictable bearing on the incidence of the disease trait in the population.

All cases of these syndromes either inherit the abnormality or fall victim thereto as a result of mutation of a gene regulating the normal biochemical counterpart of the basic defect. (Although the aberration of a normal gene or, as in the case of certain of the "inborn errors of metabolism," the loss of the active component of the gene is probably what occurs in mutation, it is now clear that in many instances mutation is a matter of position change; no alteration in the gene has occurred except one involving its position on the chromosome relative to its fellow genes.) All cases of these diseases have, of course, arisen by mutation in the more or less remote past. "Sporadic" is the designation employed clinically for those cases which occur as the result of *de novo* mutation during parental gametogenesis. The incidence of sporadic cases is inversely related to the care with which the families are studied. Because of the considerations diagrammatically indicated in Fig. 1, the incidence of sporadic (i.e., *de novo*) cases is always likely to be set abnormally high. All but one case in a family may be too mild to be identified positively as affected.

The term "heritable" was selected for the title of this review (rather than "inherited" or "hereditary") to express the fact that in a given individual the disease, although capable of being transmitted to the offspring, may not have

been inherited, but rather have arisen by mutation. Since even in the latter instance, the abnormality occurs first in the germinal product of one or the other parent, it becomes a philosophical question whether the affected individual should be said to have inherited the trait or to have become affected at his earliest conception.

The factors responsible for the original mutation in these disorders are unknown.

The terms "genotype" and "phenotype" are used, respectively, to refer to the genetic constitution of the individual and to his physical, or somatic, make-up. "Phenocopies"—clinical syndromes, of either genetic or acquired origin, which at least superficially resemble the particular hereditary syndrome under investigation—may confuse clinical and genetic studies. For example, the fetal infection accompanying maternal rubella may so influence development that loose-jointedness, arachnodactyly, and ocular and cardiovascular anomalies —a picture superficially resembling Marfan's disease—result. Careful study of the precise type of eye or vascular involvement is necessary to exclude Marfan's syndrome in such instances. In many individual instances, the four syndromes which are the main topic of this review phenocopy each other, as is evident from Table I and as will be amplified below.

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It is desirable to avoid eponyms wherever possible and it is preferable to employ designations which indicate as precisely as possible the fundamental nature of the disease entity under consideration. In the present state of our knowledge, however, there are good reasons to use eponyms for many syndromes: (1) Eponyms do not prejudice the search for the fundamental abnormality in each case. They do not conceal our ignorance of the basic defect. (2) By not using one feature of each complex syndrome as the designation, the eponym does not convey the impression that the presence of said feature is a sine qua non for the diagnosis, or that said feature occurs exclusively as a component of the particular syndrome. "Arachnodactyly" is a poor term for the Marfan disease because the fingers of many of the victims are no more spidery than those of many normal persons. Cutis hyperelastica and cutis laxa are poor terms for the Ehlers-Danlos syndrome since skin abnormalities may be relatively unimpressive in persons with striking joint hypermobility. The pity is not that eponyms are employed in these diseases but rather that there are no phonetically satisfactory or widely accepted eponyms to use in connection with disorders such as osteogenesis imperfecta and pseudoxanthoma elasticum, in which the defect is much broader in its localization than merely bone or skin, respectively.

Many individual manifestations occur in more than one of these syndromes resulting from defective connective tissue. For example: loose-jointedness with flat feet, pseudoclubfoot, habitual dislocation of joints, etc., may be a striking feature of the Marfan disease, the Ehlers-Danlos syndrome, and osteogenesis imperfecta. Hypotonicity and underdevelopment of skeletal musculature occur in the Marfan syndrome, osteogenesis imperfecta, and the Ehlers-Danlos syndrome. Impressively blue sclerae occur with Marfan's disease and, on the other hand, arachnodactyly occurs with osteogenesis imperfecta. Dissection

of the aorta and ectopia lentis occur primarily in the Marfan syndrome but also occasionally in the Ehlers-Danlos syndrome. Because of this overlap as to individual components it is desirable, in the absence of a specifically descriptive title, to refer to these diseases by eponyms or by some relatively noncommittal name, rather than by a single manifestation which may be neither specific for the syndrome nor an invariable feature.

In summary, it may be pointed out that, as is dramatically illustrated by these hereditary disorders of connective tissue, one gene may have many effects. But, countrariwise, many different genes may individually or in combination produce a particular abnormal trait. The resulting complexities of clinico-genetic analysis are apparent.

REFERENCES

1. Gowers, W. R.: Abiotrophy, Lancet **1**:1003, 1902.
2. Snyder, L. H.: Principles of Gene Distribution in Human Populations, Yale J. Biol. & Med. **19**:817, 1947.
3. Follis, R. H., Jr.: Osteogenesis Imperfecta, a Connective Tissue Diathesis, J. Pediat. **41**:713, 1952.
4. Gruneberg, H.: Animals Genetics and Medicine, New York, 1947, Paul B. Hoeber, Inc.
5. Caspari, E.: Pleiotropic Gene Action, Evolution **6**:1, 1952.
6. Burnet, Sir Macfarlane: The Riddle of Influenza Virus, Endeavour **14**:5, 1955.
7. Jeghers, H., McKusick, V. A., and Katz, D. H.: Generalized Intestinal Polyposis and Melanin Spots of the Oral Mucosa, Lips and Digits, New England J. Med. **241**:993, 1031, 1949.
8. Fisher, R. A.: The Genetical Theory of Natural Selection, Oxford, 1930, Clarendon Press.
9. Neel, J. V., and Shull, W. J.: Human Heredity, Chicago, 1954, University of Chicago Press, pp. 66 and 75.

HERITABLE DISORDERS OF CONNECTIVE TISSUE

II. The Biology of Normal Connective Tissue*

Victor A. McKusick, M.D.

Baltimore, Md.

From the Department of Medicine, The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital

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CONNECTIVE tissues, the supporting structures of the body, include cartilage, ligaments, tendons, fascia, joint capsules, the subepidermal portions (corium) of the skin, important elements of the heart valves and aorta and smaller blood vessels, and finally bone. In general, connective tissue consists of cellular and fibrous constituents embedded in the so-called ground substance. Reference is made to textbooks of histology (e.g., Fig. 45 of ref. 21) for graphic presentation of the structural interrelationships of these elements.

THE CELLULAR ELEMENTS

Virtually all the other endogenous elements of connective tissue are elaborated by the fibroblast, the main cellular constituent of connective tissue, or by its congeners, such as the osteoblast and the chondroblast. Other cellular elements include the mast cell and wandering cells such as macrophages. (The mast cell, which has long been implicated in the formation of heparin, has been thought to be concerned also in the formation of hyaluronic acid.[23]) Very recently some information has accumulated about the enzymatic processes involved in the formation of acid mucopolysaccharides.[20] In general, however, details of the biochemical processes by which the fibroblast manufactures the other elements of connective tissue are obscure.

THE FIBROUS CONSTITUENTS

The fibrous constituents of connective tissue comprise two main groups: collagenous and elastic. The reticulin fiber would be classified by some as a separate category (see below) but most consider it a member of the collagen group although its precise relationship to the classical collagen fiber is moot.

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*The author must acknowledge much assistance in the preparation of this brief survey from the reviews and symposia indicated in the list of references and from the lecturing staff of the Course in Biophysical and Biochemical Cytology conducted by Prof. F. O. Schmitt, Dr. Jerome Gross, and colleagues at the Massachusetts Institute of Technology, June 12-24, 1955.

Collagen must be defined in terms of its properties. It is a fibrous protein occurring in wide, straight, unbranching white bundles which possess high tensile strength and low elasticity. It has characteristic 640 Å periodicity by small angle x-ray diffraction and by electron microscopy. It contains two unique amino acids, hydroxyproline and hydroxylysine. The former is in relatively large amounts and is used in quantitative determination of collagen.[12,13] It contains large amounts of glycine. Aromatic and sulfur amino acids are present only in low concentration.

The biologic importance of collagen in the individual organism and in the phylogenetic series is tremendous. Collagen represents approximately 30 per cent of the total protein of the human body. In the vertebrate animal it is what cellulose is to plants. As the matrix of bone[39b,33] it was referred to as "ossein" in the older literature. Even the vitreous humor of the eye contains fibers with the properties of collagen, the so-called "vitrosin" of Gross.[26] That it is not limited to vertebrates is indicated (as merely one example) by the fact that collagen is the skeleton of the invertebrate sponge familiar in household and other usage.

The economic importance of collagen dates back to prehistory when the manufacture of leather[8] and glue was first undertaken. Isinglass, now almost completely replaced by synthetic substitutes, was also collagenous in origin. It was in leather manufacture that one property of collagen, thermal shrinkage (at 60° to 65° C.) was discovered and used in judging adequacy of tannage.

The importance of collagen in pathology will be evident to a medical audience since the concept of "collagen vascular diseases" has seemingly gained such wide acceptance. Further medical implications appear to be represented by certain of the hereditary disorders of connective tissue, under discussion here.

These implications—biologic, economic, and medical—have been responsible for very extensive investigations of the nature of collagen[1,2,7,9,11] by scientists of diverse interests and perspectives. The result has been, in the past at least, a situation like the elephant which was examined by the six blind men. Recently several excellent symposia have effected a synthesis of the diverse bits of information.

Neither the ultrastructure of collagen nor the mode of its formation,[11m, 40] is established in full detail or beyond debate. A concept which perhaps is most consistent with the information available is as follows: The building blocks of collagen, the tropocollagen unit in the terminology of Gross, Highberger, and Schmitt,[41] is elaborated by the cell, possibly intracellularly, and is extruded into the extracellular environment where ionic and other conditions favor its orderly linear aggregation into the collagen fibril. The tropocollagen unit is thought to have a length (and periodicity) of about 2,000 Å, and the 640 Å periodicity of the finished product is conceived by Schmitt and collaborators as the result of a staggering of the building blocks in their lining-up side to side. The discovery that it is possible to solubilize collagen and then reconstitute it from solution was responsible for much of this concept. Physicochemical studies indicate that the tropocollagen unit is a thin, rigid rod with a molecular weight of 300,000 to 310,000 by osmolarity and by light scattering, and with dimensions

of about 14 Å by 2,000 Å.[25] Although the larger collagen aggregates are very little extensible and in no way approach elastic fibers in this respect, electron optical observations of collagen fibrils[4] indicate that considerable extensibility of these smaller units is possible. Abnormality in the fibrillar organization may be important in the genesis of the abnormal extensibility of tendons, joint capsules, and ligaments, in certain of the heredity disorders of connective tissue.

The carbohydrate content of collagen is low. What is present may be derived from ground substances playing the role of interfibrillary cement. In pure collagen, hydroxyproline is present as about 14 Gm. per 100 Gm. protein (8.6 Gm. per 100 Gm. amino nitrogen) and glycine in roughly twice as great a proportion. The polar side groups of collagen appear to be located at the areas of the bands displayed by x-ray diffraction and by electron microscopy. These are the reactive areas where stains and tanning agents operate.

The relative metabolic inertia of nonsoluble collagen is a very striking feature.[3] The turn-over rate is slightly higher in bone than in tendon, and in younger animals, but much lower than in proteins of cell and plasma. Soluble or extractable collagen,[6a] which according to the trinitarian breakdown of connective tissue elements followed here must be considered part of the ground substance, has a considerably higher rate of turnover.[5] No collagenase comparable to that produced by *Clostridia* has been demonstrated in man with the exception of the extraction by Schmitt and Sizer[27] of material with the properties of collagenase from the cells around embedded collagenous sutures.

Reticulin fibers have most of the same properties as collagen fibers, most important the 640 Å periodicity. The main difference is their small diameters, stainability by silver, and a relatively high concentration of associated polysaccharide. Reticulin fibers predominate in the embryo, and in the adult animal are relatively abundant in parenchymatous organs, in lymph nodes and spleen, around muscle bundles and fat globules, and in association with amorphous material in epithelial basement membranes. The differences from collagen fibers may be a matter of fiber size or diameter of the individual fibrils in a bundle. Given a collagen bundle and a reticulin bundle of the same over-all diameter, the reticulin bundle may stain with silver because it has a great many more component fibrils of small diameter and correspondingly greater total fibril surface area. Staining with silver is a surface phenomenon as demonstrated by Gross. Whether reticulin is precollagen or immature collagen (not to be confused with procollagen or soluble collagen) is perhaps not too important a consideration. The concept of Gross and others that it is not a progenitor of collagen is based on the fact that it is present in the adult organism seemingly without ever being transformed into collagen and that electron microscopic evidence for aggregation of reticulin fibers (of small diameter) into collagen fibers is lacking. Reticulin fibers are present in the adult organism, in the corium, for example, and are possibly present in as great absolute amounts as at any earlier stage in ontogeny. In the adult, however, the reticulin fibers are "swamped" by the preponderance of collagen fibers.

Elastic fibers[28] are large branching refractile structures, light yellow or brown depending on their age; with a high degree of extensibility; indestructi-

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bility in relation to heat, drastic pH changes, and enzymes; a low content of polar amino acids; and finally, certain distinctive tinctorial characteristics. The nature of their staining by orcein and related dyes is not at all well understood; the staining bears no relationship to pH and there is no other evidence that salt linkages are involved.[29]

Whereas collagen is present in areas where a pliant but relatively nonextensible building material is necessary (ligaments, tendons, fascia, joint capsules), elastic fibers serve important functions in areas such as the media of the aorta (where they are responsible for the compression chamber, reservoir, or *Windkessel* hemodynamic function of that structure), in the elastic cartilage of the ear, and in ligaments with large elastic components such as those of the foot and the ligamenta flava of the spine.

Chemically, elastic fibers have approximately the same concentration of nonpolar groups, such as glycine, as does collagen. However, there are virtually no polar amino acids such as hydroxyproline, glutamic, and arginine. The relative absence of reactive amino acid side-chains is probably responsible at least in part for the unique properties of elastin.

Much less is known about the ultrastructure of the elastic fiber than of the collagen fiber. Gross has found that the double helical structures earlier described by him[35] in electron photomicrographs of material derived from aorta were in fact not elastic fiber elements but trypsinogen[32] in the enzyme preparation used in removing nonelastic elements. One view[16] of the chemical constitution is that a pro-elastin core is embedded in a matrix of combined pro-elastin and elastomucin. There is produced in the pancreatic islet tissue an elastase[15,28] for which there is an inhibitor produced elsewhere in pancreas. Elastic fibers are moderately susceptible to digestion by trypsin, resistant to digestion by pepsin; this is the converse of the situation with collagen.

THE GROUND SUBSTANCE

The ground substance is the extracellular, extrafibrillar, amorphous matrix of connective tissue. It has components derived from the fibroblast such as acid mucoprotein, acid mucopolysaccharide, and dispersed (soluble or pro-) collagen, and components not elaborated locally such as water, ions, small organic molecules such as glucose, cell metabolites, plasma proteins, and others. It is important not to equate ground substance to acid mucoproteins and acid mucopolysaccharides, as has become a frequent practice, since on a quantitative basis, and possibly on a functional basis, some of the other constituents such as plasma proteins, soluble collagen, and neutral mucoproteins are more important. Another assumption which may be fallacious is that changes in serum mucoprotein (which is neutral) reflect changes in acid mucopolysaccharide of the ground substance; chemically the two are quite distinct.

Although numerous, presumedly distinct mucopolysaccharides of connective tissue have been identified, the principal ones appear to be hyaluronic acid, chondroitin sulfuric acid, and heparin. These have in common the fact that they are polymers of high molecular weight and are composed, among other

moieties, of hexosamines (glucosamine in the case of hyaluronic acid; galactosamine in the case of chondroitin sulfate) and of glucuronic acid. Chondroitin sulfuric acid comprises 12 to 14 per cent of cartilage, but with this exception the mucopolysaccharides are present only in low concentration in connective tissues. Chondroitins B and C, differing slightly from chondroitin A of cartilage, have been identified. Chondroitin sulfate B, which apparently is characterized by an absence of glucuronic acid, occurs in heart valves, tendon, aorta, and skin.[18] Metabolically mucopolysaccharides are rapidly turned over. Metachromatic staining of connective tissues, as by toluidine blue, is a function largely of mucopolysaccharides.[36,37] In the mammalian organism hyaluronidase has been identified with certainty only in testis.

TABLE I. CHARACTERISTICS OF COLLAGEN

(A partial tabulation)

CATEGORY BASED ON METHOD OF STUDY	CHARACTERISTIC FEATURES
Histologic properties[11a]	Tinctorial characteristics: Acid fuchsin—bright red staining Periodic acid and Schiff's reagent—faint red staining Silver methods—not well stained Dilute acids and alkalis—swelling
Electron microscopic features	640 Å periodicity
Chemical features	14% hydroxyproline by weight. Hydroxylysine also unique amino acid. Low content of tyrosine, methionine, and histidine. Absence of cystine and tryptophane. 1% hexosamine (associated carbohydrate)
Shrinkage characteristics	Temperature: 60°-65°C. (shrinkage to about 1/3 original length) Certain electrolyte solutions
Behavior toward enzymes	Attacked by pepsin Attacked by "collagenases" of *Clostridium histolyticum* and *Cl. welchii*[11b] Resistant to trypsin, chymotrypsin, papain, hyaluronidase
Isotope tracer studies of metabolic turnover rate	Relative metabolic inertia[3]
X-ray crystallography	Characteristic pattern(s)[1]
Immunologist	Lack of antigenicity of unaltered collagen,[14] viz., use for suture material

The importance of the ground substance is evident when one considers that it must be traversed by all materials entering and leaving the cells.[6b] The concept[7,34,42] that mucopolysaccharides function like a reactive gel of the ion-exchange resin group is an intriguing but as yet unproved concept. It is at least theoretically possible that changes in the concentration or state of polymerization might modify greatly the capacity of connective tissues to bind inorganic ions and water. Hyaluronic acid, highly hygroscopic in the purified

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state, may be concerned in water-binding by tissues. Chondroitin sulfate, because of its highly charged anionic groups, may function[11f] as a cation exchange resin.

Jackson[24] has presented data which he interprets as indicating an important role of mucopolysaccharide in the organization and certain properties of collagenous structures such as tendon. Trypsin will digest gelatin but not native collagen. The characteristic shrinkage temperature of native collagen is altered by treatment directed at the matrix.

FURTHER CONSIDERATIONS

In addition to these general features of connective tissue, which undoubtedly assists in the understanding of the heritable disorders to be discussed, there are some specific questions about the biology of connective tissue which come to mind with study of these diseases. For example, to mention only a few, in the Marfan syndrome: What does the suspensory ligament of the ocular lens have in common with the media of the aorta? What controls longitudinal growth of bone? In pseudoxanthoma elasticum: What is the nature of Brück's membrane of the eye and what does it have in common with the corium? What is the basic nature of orceinophilic staining; specifically, if it is dystrophic collagen which stains in this disease, what change has occurred to result in this tinctorial simulation of elastin? In the Ehlers-Danlos syndrome: What is responsible for the tensile strength of the skin and for its elasticity? What determines the elastic properties of the collagen and elastin molecules, and of fibers of these proteins? In osteogenesis imperfecta: What is the normal organization of apatite on collagen which accounts for the important structural properties of bone, and, in this disease, what change in collagen has occurred to disrupt the normal collagen-apatite relationship? In connection with the full discussion of each of the entities, what is known in answer to these questions and others will be presented. Unfortunately, much remains to be learned in all these areas.

REFERENCES

1. Baer, R. S.: The Structure of Collagen Fibrils, *In* Advances in Protein Chemistry **7**:69 1952 (New York, Academic Press).
2. Borasky, R.: Guide to the Literature on Collagen. Agricultural Research Adm., U. S. Dept. of Agriculture (Eastern Regional Research Lab.), Philadelphia, 1950.
3. Neuberger, A., Perrone, J. C., and Slack, H. G. B.: Relative Metabolic Inertia of Tendon Collagen in Rat, Biochem. J. **49**:199, 1951.
4. Schmitt, F. O., Hall, C. E., and Jakus, M. A.: Electron Microscope Investigations of the Structure of Collagen, J. Cell. & Comp. Physiol. **20**:11, 1942.
5. Harkness, R. D., Marko, A. M., Muir, H. M., and Neuberger, A.: The Metabolism of Collagen and Other Proteins in the Skin of Rabbits, Biochem. J. **56**:558, 1954.
6. Rothman, S.: Physiology and Biochemistry of the Skin, Chicago, 1954, University of Chicago Press. (a) Felsher, Z.: Collagen, Reticulin and Elastin, p. 391 (Chapter 17). (b) Wells, G. C.: Connective Tissue Ground Substance, p. 418 (Chapter 18).
7. Joseph, N. R., Engel, M. B., and Catchpole, H. R.: Interaction of Ions and Connective Tissue, Biochim. et Biophys. Acta. **8**:575, 1952.
8. McLaughlin, G. D., and Theis, E. R.: The Chemistry of the Leather Industry, New York, 1945, Reinhold Publishing Corp.
9. Ragan, C.: Editor, Josiah Macy, Jr. Foundation Conferences on Connective Tissues. I. (1950.) (a) Angevine, D. M.: Structure and Function of Normal Connective Tissue, p. 13. (b) Bennett, G. A.: Pathology of Connective Tissue; Fibrinoid Degeneration, p. 44. (c) Meyer, K.: Chemistry of Connective Tissue; Polysaccharides,

p. 88. (d) Perlmann, G. E.: Enzymatically Modified Ovalbumins, p. 101. (e) Ragan, C.: Effect of ACTH and Cortisone on Connective Tissues, p. 137.
II. (1951.) (a) Gersh, I.: Some Functional Considerations of Ground Substnce of Connective Tissues, p. 11. (b) Lansing, A. I.: Chemical Morphology of Elastic Fibers, p. 45. (c) Travell, J.: Pain Mechanisms in Connective Tissues, p. 86. (d) Porter, K. R.: Repair Processes in Connective Tissues, p. 126. (e) Morrione, T. G.: Regression of Scar Tissue, p. 159.
III. (1952.) (a) Lillie, R. D.: Connective Tissue Staining, p. 11. (b) Wyckoff, R. W. G.: The Fine Structure of Connective Tissues, p. 38. (c) Robb-Smith, A. H. T.: The Nature of Reticulin, p. 92. (d) Fischel, E. E.: Hypersensitivity and the Byperadrenal State, p. 117.
IV. (1953.) (a) Ashley, C. A., Schick, A. F., Arasimavicius, A., and Hass, G. M.: Isolation and Characterization of Mammalian Striated Myofibrils, p. 47. (b) Fell, H. B.: The Effect of Vitamin A on Organ Cultures of Skeletal and Other Tissues, p. 142. (c) Meyer, K.: Outline of Problems To Be Solved in the Study of Connective Tissues, p. 185.
V. (1954.) (a) Zweifach, B. W.: The Exchange of Materials Between Blood Vessels and Lymph. (b) Gaudino, M.: Interstitial Water and Connective Tissues. (c) Asboe-Hansen, G.: Hormonal Effects on Connective Tissue.

10. Slack, H. G. B.: Metabolism of Elastin in the Adult Rat, Nature **174:**512, 1955.
11. Randall, J. T.: Editor, Nature and Structure of Collagen (Symposium), New York, 1953, Academic Press.
(a) Jacobson, W.: Histological Survey of the Normal Connective Tissue and Its Derivatives, p. 6. (b) Robb-Smith, A. H. T.: Significance of Collagenase, p. 14. (c) Cruickshank, B., and Hill, A. G. S.: Histochemical Identification of a Connective Tissue Antigen, p. 27. (d) Kramer, H., and Little, K.: Nature of Reticulin, p. 33. (e) Slack, H. G. B.: Metabolism of Collagen in the Rat, p. 51. (f) Hoppey, F., McCrae, T. P., and Naylor, A.: X-ray Crystallographic Investigation of the Changes With Age in the Structure of the Human Intervertebral Disk, p. 65. (g) Armstrong, D. M. G.: Donnan Membrane Equilibrium in Collagen-Water Systems, p. 91. (h) Robinson, C.: The Hot and Cold Forms of Gelatin, p. 96. (i) Jackson, S. F., Kelly, F. C., North, A. C. T., Randall, J. T., Seeds, W. E., Watson, M., and Wilkinson, G. R.: The Byssus Threads of Mytilus edulis and Pinna nobilis, p. 106. (j) Brown, G. L., Kelly, F. C., and Watson, M.: Quantitative Paper Chromatography of Amino Acids in Collagen, p. 117. (k) Stack, M. V.: Properties of Dentine Collagen, p. 124. (l) Martin, A. V. W.: Fine Structure of Cartilage Matrix, p. 129. (m) Jackson, S. F.: Fibrogenesis in vivo and in vitro, p. 140. (n) M'Ewen, M. B., and Pratt, M. I.: Scattering of Light by Collagen Solutions, p. 158. (o) Brown, G. L., and Kelly, F. C.: Electrophoresis of Collagen Solutions, p. 169. (p) Jackson, D. S.: Chondroitin Sulphate as a Factor in the Stability of Tendon, p. 177. (q) Jackson, S. F., and Randall, J. T.: The Reconstitution of Collagen Fibrils From Solution, p. 181. (r) Consden, R.: Observations on the Composition of Human Subcutaneous Tissue, p. 196. (s) Bowes, J. H., Elliott, R. G., and Moss, J. A.: Some Differences in the Composition of Collagen and Extracted Collagens and Their Relation to Fibre Formation and Dispersion, p. 199. (t) Harkness, R. D., Marks, A. M., Muir, H. M., and Neuberger, A.: Precursors of Skin Collagen, p. 208. (u) Randall, J. T., Brown, G. L., Jackson, S. F., Kelly, F. C., North, A. C. T., Seeds, W. E., and Wilkinson, G. R.: Some Physical and Chemical Properties of Extracted Skin Collagen, p. 213. (v) Randall, J. T.: Physical and Chemical Problems of Fibre Formation and Structure, p. 232. (w) Cowan, P. M., North, A. C. T., and Randall, J. T.: High-Angle X-ray Diffraction of Collagen Fibres, p. 241. (x) Seeds, W. E.: Infra-red Absorption and Collagen Structure, p. 250.
12. Lowry, O. H., Gilligan, D. R., and Katersky, E. M.: The Determination of Collagen and Elastin in Tissues With Results Obtained in Various Normal Tissues From Different Species, J. Biol. Chem. **139:**795, 1941.
13. Neuman, R. E., and Logan, M. A.: The Determination of Collagen and Elastin in Tissues, J. Biol. Chem. **186:**549, 1950.
14. Waksman, B. H., and Mason, H. L.: The Antigenicity of Collagen, J. Immunol. **63:**427, 1949.
15. Balo, J., and Banga, I.: The Elastolytic Activity of Pancreatic Extracts, Biochem. J. **46:**384, 1950.
16. Hall, D. A., Reed, R., and Tunbridge, R. E.: Structure of Elastic Tissue, Nature **170:**264, 1952.
17. Perl, E., and Catchpole, H. R.: Changes Induced in the Connective Tissues of the Pubic Symphysis of the Guinea Pig With Estrogen and Relaxin, Arch. Path. **50:**233, 1950.
18. Meyer, K., and Rapport, M. M.: The Mucopolysaccharides of the Ground Substance of Connective Tissue, Science **113:**596, 1951.
19. Gross, J.: Connective Tissue Fine Structure and Some Methods for Its Analysis, J. Gerontol. **5:**343, 1950.

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20. Dorfman, A.: Metabolism of the Mucopolysaccharides of Connective Tissue, Pharm. Rev. **7**:1, 1955.
21. Maximow, A. A., and Bloom, W.: A Textbook of Histology, Philadelphia, 1942, W. B. Saunders Co.
22. Meyer, K., and Rapport, M. M.: Hyaluronidases, Advances Enzymol. **13**:199, 1952.
23. Asboe-Hansen, G.: The Origin of Synovial Mucin. Ehrlich's Mast Cell—a Secretory Element of Connective Tissue, Ann. Rheumat. Dis. **9**:149, 1950.
24. Jackson, D. S.: The Nature of Collagen-Chondroitin Sulfate Linkages in Tendon, Biochem. J. **56**:699, 1954.
25. Boetker, H., and Doty, P.: On the Nature of the Structural Element of Collagen, J. Am. Chem. Soc. **77**:248, 1955.
26. Gross, J., Matoltsy, A. G., and Cohen, C.: Vitrosin: A Member of the Collagen Class, J. Biophys. Biochem. Cytol. **1**:215, 1955.
27. Schmitt, F. O., and Sizer, I. W.: Personal communication.
28. Banga, I., and Balo, J.: Elastin and Elastase, Nature **171**:44, 1953.
29. Weiss, J.: The Nature of the Reaction Between Orcein and Elastin, J. Histochem. & Cytochem. **2**:21-28, 1954.
30. Bowen, T. J.: Physical Studies on a Soluble Protein Obtained by the Degeneration of Elastin With Urea, Biochem. J. **55**:766-768, 1953.
31. Bowes, J. H., and Kenten, R. H.: Summary of Published Results (1900-1946) on Amino Acid Composition of Gelatin and Collagen, Leather Manuf. Res. Assoc., pp. 1-22, 1947.
32. Gross, J.: Fiber Formation in Trypsinogen Solutions: An Electron Optical Study, J. Proc. Exper. Biol. & Med. **78**:241, 1951.
33. Blackett, N. M.: On the Organization of Collagen Fibrils in Bone, Biochim. et Biophys. Acta. **16**:161, 1955.
34. Day, T. D.: The Mode of Reaction of Interstitial Connective Tissue With Water, J. Physiol. **109**:380-391, 1949.
35. Gross, J.: The Structure of Elastic Tissue as Studied With the Electron Microscope, J. Exper. Med. **89**:699, 1949.
36. Braden, A. W. H.: The Reactions of Isolated Mucopolysaccharides to Several Histochemical Tests, Stain Technol. **30**: 19, 1955.
37. Gomori, G.: The Histochemistry of Mucopolysaccharides, Brit. J. Exper. Path. **35**:377, 1954.
38. Hass, G. M.: Elastic Tissue, Arch. Path. **27**:334, 543, 1939.
39. (a) Reifenstein, E. C., Jr., editor: Metabolic Inter-relations, With Special Reference to Calcium. Transactions of the Fifth Conference, Josiah Macy, Jr., Foundation, New York, V. 1953. (b) Robinson, R. A., and Watson, M. L.: Electron Micrography of Bone, p. 72.
40. Gross, J., Highberger, J. H., and Schmitt, F. O.: Some Factors Involved in the Fibrogenesis of Collagen In Vitro, Proc. Soc. Exper. Biol. & Med. **80**:462, 1952.
41. Gross, J., Highberger, J. H., and Schmitt, F. O.: Collagen Structures Considered as States of Aggregation of a Kinetic Unit. The Tropocollagen Particle, Proc. Nat. Acad. Sc. **40**:679, 1954.
42. Gray, J.: The Properties of Inter-cellular Matrix and Its Relations to Electrolytes, Brit. J. Biol. **3**:167-187, 1926.

EVALUATION OF CURRENT THERAPY IN CEREBRAL VASCULAR DISEASE

JOSEPH F. FAZEKAS, M.D., JACK KLEH, M.D., AND RALPH W. ALMAN, M.D.

WASHINGTON, D. C.

From the Georgetown and George Washington University Medical Divisions, District of Columbia General Hospital

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ONE of the most pressing problems in medicine is the management of the increasing numbers of patients with overt manifestations of cerebral dysfunction associated with vascular disease. Numerous neurologic syndromes are the result of occlusion of diseased cerebral vessels with curtailment of blood supply below the minimum requirements of a nonsilent area of the brain.[1] Not only does the central nervous system react acutely to reduction of its blood supply below critical levels, but impairment of function to a degree which might be trivial in other organs is commonly manifested in dramatic fashion in the case of the brain. It is difficult to say with certainty whether in the above instances the cerebral vessels are more severely involved by atherosclerosis than those of other organs or whether their involvement is not remarkable in degree but is simply more obvious.

The precise nature of the relationship between diffuse cerebral atherosclerosis and generalized cortical dysfunction is not clear. Studies of cerebral hemodynamics and metabolism in various age groups demonstrate a progressive reduction of cerebral blood flow and oxygen consumption with advancing years, even in the absence of obvious functional impairment.[2] Other data indicate that within certain limits even further acute reduction of cerebral blood flow can be induced in elderly subjects without the appearance of untoward symptoms.[3] The reduced cerebral blood flow of many aged individuals may therefore exist coincidentally with diminished cerebral oxygen consumption and impaired mental function due to reduced cellular activity of independent pathogenesis.

At the present time there is no successful method for the prevention or reversal of cerebral atherosclerosis. The therapeutic and corrective measures employed in the management of patients with acute and chronic cerebral vascular disturbances include administration of vasodilating agents, cerebral stimulants

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and depressants, and anticoagulants. Hypotensive agents are also frequently given to reduce the elevated blood pressure commonly present in patients with cerebral vascular disease. Finally, rehabilitative measures directed to correct, as far as possible, the physical disabilities resulting from occlusion of larger cerebral vessels are at present receiving much attention. This report is an attempt to evaluate critically the various therapeutic measures mentioned above.

VASODILATING AGENTS

Whenever the circulation to a portion of the brain becomes impaired by occlusion of a cerebral artery, several compensatory mechanisms may increase delivery of blood to the involved region. The duality of the cerebral circulation (carotid and vertebral arteries and their intercommunication) permits a redistribution of blood flow which may possibly limit or prevent the development of cerebral infarction due to occlusion in or below the circle of Willis. Adams[4] has demonstrated the probable existence of collateral circulation via intracerebral capillaries and meningeal-cortical loops which may become significantly functional due in part to changed pressure differentials. Local hypoxia and the accumulation of metabolic intermediates resulting from cerebral ischemia may dilate regional collateral vessels and thus improve circulation of the involved area. The transient nature of many attacks of cerebral ischemia due to organic arterial occlusion possibly may result in part from activation of these mechanisms.

The hope is generally entertained by the practicing physician that restoration of the cerebral circulation with vasodilating agents will improve cellular metabolism and cerebral function in patients with cerebral vascular insufficiency. Experience indicates, however, that most of the currently available vasodilating agents are without significant effect, perhaps because irreversible brain damage has resulted before the agent can be administered. Furthermore, most vasodilators studied (histamine,[5] nicotinic acid,[6] papaverine,[7] procaine,[8] and alcohol,[9]) have nonspecific effects, and relaxation of cerebral vessels may occur simultaneously with, or reflexively because of, a general reduction of mean arterial pressure with no resulting improvement in total cerebral blood flow. Moreover, dilatation of the cerebral vessels, whether reflex or representing a direct response to a drug, may be confined to those vessels least affected by disease; and if hypotension is also induced, the net effect may be an even greater degree of ischemia of the areas of the brain supplied by rigid, narrowed vessels.[10]

An exception to the above to some extent may be carbon dioxide, which appears to be the most efficacious agent available for increasing quantitatively the rate of cerebral blood flow by reduction of cerebral vascular resistance.[11] The inhalation of 5 per cent CO_2 causes, in addition, a moderate increase of the mean arterial blood pressure. Unfortunately, side-effects, such as hyperpnea and anxiety, prevent its continuous administration. The increase in rate of cerebral blood flow is not as marked in elderly atherosclerotic subjects as in younger persons but nevertheless is of significant magnitude.[12] It is possible, therefore, that even elderly patients suffering from acute cerebral thrombosis

may derive some benefit from the intermittent inhalation of 5 per cent CO_2 if instituted early enough.

There has been much discussion concerning the value of stellate ganglion block in overcoming spasm of regional vessels believed to be associated with acute cerebral infarction.[13] Forbes and Cobb[14] have demonstrated that vasomotor influences on tonus of cerebral vessels are relatively weak. The concept of neurogenic spasm of cerebral vessels secondary to infarction is debatable in view of the well-recognized fact that chemical changes (hypoxia, increased CO_2 tension, and the production of acid metabolic intermediates from glycolytic processes) operate to dilate cerebral capillaries and arterioles and exert a much greater influence than whatever neurogenic factors may tend to constrict these vessels. In our experience, the incidence of improvement following stellate ganglion block in patients with acute cerebral thrombosis has not been significantly different from that of spontaneous remission in a similar group of untreated patients.[15] Similar observations on a larger series of patients has recently been reported by Millikan.[16]

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As previously indicated, there is no clear relationship between the rate of cerebral blood flow and the cellular dysfunction so often noted in elderly persons presumably having cerebral atherosclerosis. Such subjects, although they may respond to 5 per cent CO_2 inhalation with a significant increase in cerebral blood flow, do not show in general any significant change in cerebral oxygen consumption nor has there been demonstrated any evidence of improvement in their mental status due to CO_2 inhalation.[12] This finding should not be entirely unexpected since the cerebral venous blood oxygen tension of elderly atherosclerotic subjects with overt manifestations of cerebral dysfunction is usually only slightly reduced from values noted in normal subjects and much more oxygen is available to cerebral cells than is utilized.[17] In fact, actual experiment has demonstrated in elderly subjects with reduced cerebral oxygen consumption and cerebral blood flow that a further reduction of the latter produced by acute hypotension is associated with a widening of the cerebral arteriovenous oxygen difference, and there is no significant change in cerebral metabolic rate.[3] In other words, the metabolism of cerebral cells may be irreversibly, or at least independently, impaired in such cases rather than merely suppressed by the reduced oxygen delivery, and simply increasing oxygen delivery by improving blood flow cannot be expected to correct the cellular metabolic defect.

CEREBRAL STIMULANTS AND DEPRESSANTS

Drugs falling into the above categories are frequently used in the symptomatic management of subjects with generalized cerebral vascular insufficiency. It is unfortunate that so little is known regarding the mechanism of action of these drugs, and of the processes referred to as stimulation and depression. For the most part, the effects of these drugs can be evaluated only by clinical observations and psychologic tests, neither of which is completely reliable. The day-to-day spontaneous variations in the intensity of the manifestations make critical evaluation of drug therapy extremely difficult.

It is in those instances where malfunctioning of cerebral cells produces clinical manifestations commonly attributed to diffuse atherosclerosis that cerebral stimulants and depressants are often used. Such clinical disturbances cover a broad range of psychiatric and subjective neurologic symptomatology. Behavior may vary between agitation and apathy. Personality and intellectual deterioration are usually considered characteristic of the syndrome. Neurologic symptoms, such as dizziness and weakness, are usually nonlocalizing. Cerebral stimulants, such as Metrazol (pentylenetetrazol) and Meratran (pipradrol hydrochloride), are administered in the belief that many of the cortical cells of senile individuals are functioning at suboptimal levels because of either a previous ischemic insult or even an unrelated metabolic defect. Whether it is possible to restore toward normal the energy production or utilization of metabolically deficient cerebral cells by the use of stimulants is open to question. There is no evidence to indicate that those cells functioning least effectively are at all influenced by cerebral stimulants; in fact, it is more reasonable to expect that the normal cells may be most reactive. Of course, nothing could be accomplished if these "depressed" cells were glial cells which had replaced neuronal elements. If the reduced energy production or utilization were due to enzymatic deficiency of cerebral cells, the stimulant, to be effective in improving function, would have to act specifically on the "bottleneck" enzyme complex limiting energy production. Such enzyme-specific action might conceivably result in an increase of total cerebral oxygen consumption, certainly in the case of the senile brain, but this has not been demonstrated.[18] It may be, however, that the functional activity of the brain requires so small a proportion of the total cerebral oxygen consumption that its specific requirements are not measurable by available techniques.[19] The increase in electrical activity of the brain of elderly subjects observed following the administration of stimulant drugs is not necessarily indicative of the production of useful energy by impaired cerebral cells. In general, there appears to be insufficient data to justify the use of these drugs for the management of patients with generalized cerebral dysfunction.

Cerebral depressants (sedative drugs) are frequently employed to control insomnia, anxiety, confusion, or the agitation often manifested by patients with generalized cerebral dysfunction. Elderly atherosclerotic patients are notoriously subject to insomnia, nightmares, and even nocturnal confusion and disorientation. Since it is not likely that circulatory maladjustment can be so severe as to produce these symptoms by causing cerebral ischemia,[20] it may be more reasonable to attribute them to partial wakefulness resulting from excessive dozing or even sleep during the day. The periodic nocturnal confusion and disorientation may be analogous to nightmares and indeed have been so described by such patients in their lucid intervals. Administration of barbiturates may be indicated for symptomatic therapy; unfortunately, these drugs, even in normal therapeutic amounts, occasionally precipitate confusion and disorientation. Although no satisfactory explanation for this phenomenon has been advanced, it may well be related to the reduced cerebral metabolic activity of these subjects, with slight further cortical depression caused by the drug

being sufficient to induce the equivalent of the excitement stage of anesthesia. In the presence of increasing mental disintegration in atherosclerotic patients, it may be wise to discontinue the administration of sedatives for several days before concluding that cerebral deterioration is progressing spontaneously.

At present, chlorpromazine and reserpine are being widely used in the management and treatment of both the psychotic and psychoneurotic manifestations of subjects with generalized cerebral vascular insufficiency. Favorable responses have been reported, particularly in those patients with increased psychomotor activity. In moderate doses (0.3 to 0.8 mg. for reserpine; 25 to 300 mg. for chlorpromazine), these drugs do not change the cerebral oxygen utilization significantly. Side effects, such as vascular collapse, jaundice, photosensitivity, agranulocytosis, lactation, and the development of a Parkinsonism-like syndrome may complicate their prolonged administration.

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HYPOTENSIVE AGENTS

It has been recommended that blood pressure be reduced in all hypertensive subjects except those with cerebral vascular disease.[21] This reservation is based upon the belief that relative hypotension may constitute a serious hazard in such cases. Not only does the probability of resulting cerebral ischemia or thrombosis seem to be exaggerated by those insisting on this limitation, but such a criterion for administering or withholding hypotensive drugs appears somewhat illogical in view of the fact that extreme degrees of cerebral atherosclerosis may produce no clinical signs.

Hypertension is generally recognized as accelerating the development of vascular disease and its complications, and in hypertensives the peak incidence of cerebral thrombosis appears at a somewhat younger age than in normotensive persons. Cerebral hemorrhage in elderly subjects, a less common vascular accident than thrombosis, occurs almost exclusively with diastolic hypertension. It is reasonable to anticipate that by reduction of blood pressure in patients with overt manifestations of cerebral vascular disease, complications may be delayed or prevented, and it would seem worth while to accept the calculated risk of precipitating further thrombosis or ischemic infarction by reducing blood pressure in these subjects. However, the risk should be minimized by not attempting to reduce the elevated blood pressure to normotensive levels even though total cerebral blood flow might not be reduced by such efforts.[22]

Pathologists have stressed the fact that cerebral vessels are not uniformly involved in atherosclerosis of the brain. Certain vessels ultimately derived from the same major channel may show marked degenerative changes, while others may appear to possess nearly unimpaired elasticity, and intermediate gradations may also be present. The compensatory cerebral vasodilatation associated with blood pressure reduction achieved by any means may well protect cerebral areas supplied by whatever vessels have retained their elasticity, while areas supplied by rigid or partly rigid vessels may be further compromised.[23-25]

Although both clinical and laboratory evidence has shown that within the

limits of experience to date, significant blood pressure reduction can usually be gradually accomplished in elderly hypertensives without harmful effects,[26] there can be no question that a critical point exists for each individual, below which hypotension will cause cerebral ischemia.[3] This point may be reached at a higher level of blood pressure in the atherosclerotic subject. Therefore, there may be more potential loss than gain by uncritical attempts to produce normotension in hypertensive atherosclerotic patients, and by the use of agents that may induce precipitous reductions of pressure.

Before selecting from among the many hypotensive agents, it is important to consider their effects upon compensatory vascular mechanisms protecting the cerebral blood supply. One of the most important of these mechanisms is that which stabilizes the cerebral circulation in the presence of postural changes. In normal subjects, assumption of the upright posture is associated with (1) increased peripheral vasomotor tone which compensates in part for the hydrostatic reduction in intracranial pressure head, and (2) partial compensation by cerebral vasodilatation.[24] The response to postural changes may be unpredictable in hypertensive subjects. The majority of such individuals do react in the normal fashion; however, not infrequently in those with atherosclerosis there may be no change in peripheral vasomotor tone, and in a few, acute orthostatic hypotension may occur.[3]

Because cerebral vascular disease is likely not only to have produced a reduction of cerebral blood flow but also to be associated with impairment of postural reflex activity, it would seem particularly undesirable to administer those hypotensive agents which themselves may cause further interference with these compensatory mechanisms.

Production of true hypotension for aiding hemostasis in certain types of surgery may be excessively dangerous in the presence of cerebral vascular disease. Experience to date in reconstructive and neurosurgery has been largely confined to individuals in younger age groups who are relatively unlikely to have clinically significant degrees of cerebral atherosclerosis; the same may be said for cardiac surgery facilitated by hypothermia, induction of which is usually aided by "lytic" drugs which cause marked blood pressure reduction. Although generally favorable results have made hypotensive and refrigeration anesthesia acceptable, we know of no studies comparing incidence of complications (particularly with reference to cerebral thrombosis) in young and in elderly subjects. It would certainly seem, however, that acute hypotensive procedures are always to be avoided, when possible, in patients known or reasonably expected to have cerebral atherosclerosis. Cerebral infarction is too high a price to pay for a bloodless field.

A questionable exception to the general inadvisability of rapid blood pressure reduction in the presence of cerebral vascular disorders may exist in the case of spontaneous cerebral hemorrhage with marked hypertension. There seems to be no ground for basing an opinion as to the relative importance of aggravating by blood pressure reduction the existing impairment of cerebral circulation secondary to greatly increased intracranial pressure, or of improving this situation by retarding active bleeding. Theoretically some means of reducing

intracranial pressure should be applied simultaneously with blood pressure reduction, but how much to reduce either or both is not known.

ANTICOAGULANTS

The lack of enthusiasm for the use of anticoagulants in cerebral vascular disturbances is principally due to the dangers of hemorrhage, particularly if the diagnosis is erroneous.

The pioneer work of Wright[27] has demonstrated, however, the value of anticoagulants in some of the above disturbances. In patients with rheumatic heart disease and myocardial infarction, Wright observed a striking reduction in the incidence of cerebral emboli during anticoagulant therapy. He is of the opinion that anticoagulants may prove useful in cerebral thrombosis in that they may prevent the propagation of the original thrombus and the development of additional thrombi in other vessels and may encourage the more rapid dissolution of the original thrombus. Millikan has also noted favorable responses to anticoagulant therapy in patients with paroxysmal attacks of cerebral dysfunction resulting from partial insufficiency of the basal or carotid arteries.[28]

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In patients with cerebral thrombosis, there are insufficient data to justify any conclusions regarding the efficacy of anticoagulants. In such patients, in addition to the danger of hemorrhage, deterrents to the use of anticoagulants have also been the uncertain prognosis, the frequent coexistence of hypertension, the need for perhaps lifetime administration, as well as the high cost of prolonged laboratory and clinical supervision. In view of the fact that the majority of patients with clinical evidence of cerebral vascular disease have cerebral thrombosis, well-controlled studies with anticoagulants are indicated, particularly in relatively young subjects. The problem of co-existing hypertension, as previously mentioned, may be satisfactorily managed by the cautious reduction of blood pressure with hypotensive agents.

There appears to be little justification for the use of anticoagulants in patients with cerebral dysfunction associated with diffuse cerebral vascular disease. Even if it were granted that cortical dysfunction were due to diffuse cerebral vascular disease, anticoagulants would be of little avail if numerous infarcts were caused by intimal arterial thickening or atheromatous placques rather than blood coagulae. In any event, improvement in cortical function could not be expected from anticoagulant therapy, but at best only arrest of deterioration.

REHABILITATION

Of all the therapeutic modalities now available, rehabilitation offers most to the patient with cerebral vascular disturbances. It is not our intention to discuss the techniques of various rehabilitative procedures but rather a modern concept of rehabilitation and the deficiencies in execution of most plans.

Unfortunately most rehabilitation programs are incomplete or are so expensive that they are beyond the means of the majority of patients. To a considerable extent, the incompleteness is due to a lack of interest in the total care

of the disabled patient, and lack of optimism concerning his future. Many physicians, interested chiefly in organ pathology, give little consideration to the total problem of the individual incapacitated by cerebral vascular disease. There is still competition to avoid supervisory control of this type of patient. Even at large teaching centers, from which may stem the success or failure of future rehabilitation programs, the concept of total patient care may be treated perfunctorily or ignored completely.

A practical remedy is the education of physicians in the great need for and value of complete rehabilitation programs. One of the more satisfactory solutions to the necessarily high cost of rehabilitation might be specifically designed rehabilitation insurance plans offered on a voluntary basis, making available complete facilities rather than monetary compensation.

The high cost of complete rehabilitation, although fully justified if even a few patients obtain physical benefit, make it highly desirable to be able to select from the many patients with cerebral vascular disease those with the best rehabilitative capacity. At present we can assess their capabilities only by working with these people and trying to develop their remaining resources. Certainly, it is generally recognized that age alone is no criterion of the individual's potentialities; neither does the degree of physical disability immediately resulting from his vascular disease always have isolated prognostic value. A large number of subjects with cerebral thrombosis have been studied to determine the degree of correlation between the rate of cerebral blood flow and metabolism and their subsequently evaluated rehabilitative potentialities.[29] No significant correlation was found to exist; subjects with relatively low cerebral blood flow and metabolism frequently made better progress than those with more normal values. This result might have been anticipated since such measurements reveal only total cerebral blood flow and metabolic rates and do not reflect localized changes in the brain. Perhaps it is fortunate that there are no objective measurements which will permit functional prognosis since the psychotherapeutic value of even those endeavors failing to produce satisfactory physical improvement may in many instances be sufficient to compensate for the efforts expended.

There are several factors other than physical capabilities which make up the patient's rehabilitation potentialities. Without question, the most important determinant in achieving maximum rehabilitation is the degree of the patient's motivation and the ability of the staff to activate and maintain optimism at a high level. This is probably one of the foremost reasons for initiating rehabilitative measures as soon after a cerebral vascular accident as possible since the longer such encouragement is neglected, the more difficult it is to stimulate these patients to improve their condition. The problem of motivation is particularly difficult with members of the indigent population since they are often reluctant to give up the attention they receive in the hospital and the security from the welfare source. In many instances their families, having been temporarily relieved of the onus of continued care, are hesitant to assume again this responsibility, thus contributing greatly to an apathetic attitude on the part of the patient.

As with any other form of therapy, the sooner rehabilitative measures are initiated, the more rapid and complete is the degree of physical improvement. That organic and mental deterioration rapidly result from neglect and restricted activity is well documented.[30] Even healthy young adults who are immobilized show within a very short period of time a negative nitrogen balance and muscle atrophy, a negative calcium balance and osteoporosis, poor vascular tone, and marked changes in behavior. One might expect that similar and even more devastating deterioration would result from the enforced immobilization of elderly subjects with cerebral vascular disease.

Proper evaluation of the patient's problems cannot be made by individual consultation but only by group deliberation. Regardless of the number of specialists available, unless they work together as a team the patient is unlikely to achieve his maximum degree of rehabilitation. Only too frequently the internist concerns himself with medical complications accompanying cerebral vascular disease, and not until he is ready to discharge the patient does he remember to call in the physiatrist. Once the patient has been referred, the physician in charge frequently abandons continued interest. Many times the physical and occupational therapists are not aware of the patient's problems and of the therapeutic objectives. Neurologists for the most part are not, or may not wish to be, consulted, and frequently no one bothers to make inquiries about the patient's social and financial status. Yet it is generally agreed that if only one important aspect of total patient care is neglected, no matter how conscientiously and vigorously the rest are pursued, rehabilitative efforts may fail unnecessarily.

The responsibility for directing and coordinating the rehabilitation program should rest with the physiatrist. The patient should be seen regularly by the internist, neurologist, psychologist, nurse, and social worker, and his problems jointly discussed and the therapeutic program outlined. The internist should survey the general condition of the patient and correct, in so far as possible, existing medical disturbances. He must familiarize the team with any complications and with the patient's therapeutic regimen. Too often these patients may be given sedatives by one physician just before maximum alertness would be desirable for consultation by another, or receive recumbency doses of hypotensive agents that cause orthostatic collapse when ambulation is attempted. Even the problem of weight reduction is often completely neglected. The neurologist should be consulted for a definitive diagnosis and to follow the progress of the lesion. It no longer suffices to state that the patient has had a "cerebral vascular accident," or even "cerebral thrombosis." It is important to designate the specific vessel involved and the neurologic disturbances present. Certainly the problems of rehabilitating a patient with middle cerebral artery thrombosis are quite different from those encountered with thrombosis of the posterior inferior cerebellar artery. The psychologist should evaluate the patient's mental capabilities and any changes in attitude so that vocational rehabilitation can be geared to his potentialities. The nurse, an important member of the team, must be aware of the therapeutic objectives and encourage the patient to continue the activities he has been taught in the rehabilitation

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area. Because it is often much easier and faster for the nurse to wait on the patient than to encourage him to be self-sufficient, acquisition of facility and self-confidence may be retarded. The physiatrist should call other specialists, if their services are required. After the plan of treatment is decided upon, meetings should be held regularly by all those participating in order to discuss progress and future management.

Hospital stay, because of expense and the importance of returning the patient to his own environment as soon as possible, should not be unnecessarily prolonged. Before discharge, however, all arrangements for continued and complete care should be made. These requirements are directed to a large extent by the social and financial status of the patient. Failure of adequate cooperation by responsible social agencies may neutralize all prior accomplishments. This is most likely to occur in the case of middle-income patients for whom such agencies have been inadequately developed. This deficiency may well result in large numbers of taxpayers regressing into the completely indigent category; only then do they become eligible for organized welfare programs.

Families should be instructed whenever possible to participate in the therapeutic program, and provisions for home medical and nursing care made whenever feasible. Clinic visits should be regularly scheduled if the patient is ambulatory, and vocational training and diversional therapy continued. Optimum results are obtained when the patient is followed by the same rehabilitation team that initiated his hospital program.

For some time it has been generally recognized that in order efficiently to manage patients with neoplastic diseases, it was necessary to establish tumor boards. Such boards consist of various specialists who, in conference rather than in consultation, discuss the evidence necessary for an accurate diagnosis; select, outline, and direct the optimum therapeutic regimen; and periodically review the patient's progress. In view of the enormously greater numbers of individuals with chronic physical disability, in large proportion due to cerebral vascular disease, it would seem equally important to establish well-organized rehabilitation boards in institutions responsible for the initial or continuing care of such patients.

SUMMARY AND CONCLUSIONS

We have reviewed the therapeutic effectiveness of vasodilating agents, stimulants, anticoagulants, and hypotensive agents, as well as rehabilitative procedures, in patients with cerebral vascular disturbances. With the exception of carbon dioxide, vasodilators available at the present time do not increase total cerebral blood flow, and they cause relaxation of cerebral vessels only in association with a reduction of pressure. The rapid development of brain damage following ischemia makes it unlikely that therapy directed toward increasing cerebral blood flow would have any practical value in chronic cases.

The effectiveness of cerebral stimulants in patients with cortical dysfunction and generalized cerebral vascular disease is questionable from both physiologic and clinical evidence currently available.

The presence of overt manifestations of cerebral vascular disease (thrombosis) does not militate against the use of hypotensive agents. Blood pressure should, however, be gradually reduced and maintained somewhat above normal values.

Anticoagulants are effective in reducing significantly the incidence of cerebral emboli in patients with rheumatic heart disease and myocardial infarction as well as recurrent attacks from threatened occlusion of basilar and carotid arteries. Experience with these drugs in patients with cerebral thrombosis is limited. There is little justification for their use in patients with psychosis and cerebral arteriosclerosis.

Although rehabilitative procedures at present seem to be the most valuable of all therapies available to patients with cerebral vascular disease, most existing programs are incomplete or are very costly. There is a great need for the establishment of rehabilitation boards in hospitals.

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REFERENCES

1. Adams, R. D., and Cohen, M. E.: Vascular Diseases of the Brain, Bull. New England M. Center **9**:180, 1947.
2. Fazekas, J. F., Kleh, J., and Parrish, A. E.: Influence of Age and Vascular Disease on Cerebral Hemodynamics and Metabolism, Am. J. Med. **18**:477, 1955.
3. Finnerty, F. A., Jr., Witkin, L., and Fazekas, J. F.: Cerebral Hemodynamics During Cerebral Ischemia Induced by Acute Hypotension, J. Clin. Invest. **33**:1227, 1954.
4. Adams, R. D.: Mechanisms of Apoplexy as Determined by Clinical and Pathological Correlation, J. Neuropath. & Exper. Neurol. **13**:1, 1954.
5. Alman, R. W., Rosenberg, M., and Fazekas, J. F.: Effects of Histamine on Cerebral Hemodynamics and Metabolism, Arch. Neurol. & Psychiat. **67**:354, 1952.
6. Scheinberg, P.: The Effect of Nicotinic Acid on the Cerebral Circulation, With Observations on Extracerebral Contamination of Cerebral Venous Blood in the Nitrous Oxide Procedure for Cerebral Blood Flow, Circulation **1**:1148, 1950.
7. Jayne, H. W., Scheinberg, P., Rich, M., and Belle, M. S.: The Effect of Intravenous Papaverine Hydrochloride on the Cerebral Circulation, J. Clin. Invest. **31**:111, 1952.
8. Scheinberg, P., Jayne, H. W., Blackburn, L. I., and Rich, M.: Studies of Cerebral Circulatory Functions Following Intravenous Administration of Procaine Hydrochloride, Arch. Neurol. & Psychiat. **68**:815, 1952.
9. Battey, L. L., Heyman, A., and Patterson, J. L., Jr.: Effects of Ethyl Alcohol on Cerebral Blood Flow and Metabolism, J. A. M. A. **152**:6, 1953.
10. Corday, E., Rothenberg, S. F., and Putnam, T. J.: Cerebral Vascular Insufficiency, Arch. Neurol. & Psychiat. **69**:551, 1953.
11. Kety, S. S., and Schmidt, C. F.: The Effects of Altered Arterial Tensions of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men, J. Clin. Invest. **27**:484, 1948.
12. Fazekas, J. F., Bessman, A. N., Cotsonas, N. J., Jr., and Alman, R. W.: Cerebral Hemodynamics in Cerebral Arteriosclerosis, J. Gerontol. **8**:137, 1953.
13. De Takats, G.: The Controversial Use of Cervical Sympathetic Block in Apoplexy, Ann. Int. Med. **41**:1196, 1954.
14. Forbes, M. S., and Cobb, S.: Vasomotor Control of Cerebral Vessels, A. Research Nerv. & Ment. Dis., Proc. **18**:201, 1938.
15. Parrish, A. E.: Unpublished data.
16. Millikan, C. H.: Cerebral Vascular Diseases, edited by Irving S. Wright and E. Hugh Luckey, New York, 1955, Grune & Stratton, p. 91.
17. Fazekas, J. F., Alman, R. W., and Bessman, A. N.: Cerebral Physiology of the Aged, Am. J. M. Sc. **223**:245, 1952.
18. Fazekas, J. F., and Kleh, J.: Unpublished data.
19. Fazekas, J. F., Graves, F. B., and Alman, R. W.: The Influence of Thyroid on Cerebral Metabolism, Endocrinology **48**:169, 1951.
20. Kety, S. S.: In Problems of Consciousness, Transactions of Third Conference, Sponsored by the Josiah Macy, Jr., Foundation, New York City, March 10-11, 1952.
21. Smirk, F. H.: The Management of Hypertension With Special Reference to the Methonium Compounds. Television Symposium on the Management of Hypertension, sponsored by Wyeth Laboratories, Philadelphia, Sept. 23, 1954.

22. Kleh, J., and Fazekas, J. F.: The Effects of Hypotensive Agents on Subjects With Cerebral Vascular Insufficiency, Am. J. Gerontol. (In press.)
23. Kety, S. S., King, B. D., Horvath, S. M., Jeffers, W. A., and Hafkenschiel, J. H.: The Effects of an Acute Reduction in Blood Pressure by Means of Differential Spinal Sympathetic Block on the Cerebral Circulation of Hypertensive Patients, J. Clin. Invest. **29**:402, 1950.
24. Scheinberg, P., and Stead, E. A., Jr.: The Cerebral Blood Flow in Male Subjects as Measured by the Nitrous Oxide Technique. Normal Values for Blood Flow, Oxygen Utilization, Glucose Utilization, and Peripheral Resistance, With Observations on the Effect of Tilting and Anxiety, J. Clin. Invest. **28**:1163, 1949.
25. Alman, R. W., Rosenberg, M., and Fazekas, J. F.: Effects of Histamine on Cerebral Hemodynamics and Metabolism, Arch. Neurol. & Psychiat. **67**:354, 1952.
26. Bessman, A. N., Alman, R. W., and Fazekas, J. F.: Effect of Acute Hypotension on Cerebral Hemodynamics and Metabolism of Elderly Patients, Arch. Int. Med. **89**:893, 1952.
27. Wright, I. S., and McDevitt, E.: Cerebral Vascular Diseases: Their Significance, Diagnosis and Present Treatment, Including the Selective Use of Anticoagulant Substances, Ann. Int. Med. **41**:682, 1954.
28. Millikan, C. H., Siekert, R. G., and Shick, R. M.: Studies in Cerebrovascular Disease. III. The Use of Anticoagulant Drugs in the Treatment of Insufficiency or Thrombosis Within the Basilar Arterial System, Proc. Staff Meet., Mayo Clin. **30**:105, 1955.
29. Fazekas, J. F., and Buchanan, J.: Unpublished data.
30. Deitrick, J. E., Whedon, G. D., and Shorr, E.: The Effects of Immobilization Upon Various Metabolic and Physiologic Functions of Normal Men, Am. J. Med. **4**:3, 1948.

DEPRESSION OF CHOLESTEROL LEVELS IN HUMAN PLASMA FOLLOWING ETHYLENEDIAMINE TETRACETATE AND HYDRALAZINE

H. Mitchell Perry, Jr., M.D., and Henry A. Schroeder, M.D.

St. Louis, Mo.

From the Hypertension Division, Department of Internal Medicine, Washington University School of Medicine and Barnes Hospital, St. Louis, Mo.

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INTRODUCTION

CERTAIN transition metals alter the ability of rat liver to incorporate acetate tagged with C_{14} into cholesterol and fatty acid molecules both in vivo and in vitro.[1] Moreover, ethylenediamine tetracetate (EDTA) and another chelating agent, 8-hydroxyquinoline, change the rates of this pair of syntheses.[2] EDTA produces loss of subcutaneous fat in rats[3] and prevents hepatic cholesterolosis in rabbits fed cholesterol.[4] In addition, EDTA lowers blood pressure in experimental renal hypertension[5]; however, the vasoactivity of EDTA following its combination with transition and related elements depends on the strength of the metallic bond involved.[5] Hydralazine (1-hydrazinophthalazine), which also has a strong affinity for certain transition metals,[6] lowers plasma cholesterol in human beings.[6] Moreover, hydralazine is one of several chemically dissimilar antihypertensive compounds, including thiocyanate,[7] nitroprusside,[8] azide,[9] and mercaptans,[10,11] which bind metallic ions. Some of these compounds affect certain renal enzyme systems, as do some of the metals with which they combine.[12] In view of these effects, a trial of EDTA was given to patients with atherosclerosis and/or hypertension in an attempt to lower plasma cholesterol and/or blood pressure. Preliminary short-term results, primarily following parenteral administration, are reported below. The fall in cholesterol is compared with that observed following the oral use of hydralazine over a longer interval.

METHOD

A total of 145 patients is considered in this paper. They are divided into three mutually exclusive groups on the basis of the medication used and its route of administration. The first group received parenteral EDTA, the second, oral EDTA, and the third, oral hydralazine.

The 22 patients who received from 3 to 27 Gm. of intravenous calcium di-

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sodium EDTA* in Barnes Hospital are discussed in some detail. Their daily intake varied from 1 to 12 Gm. and the total period of administration from one to eleven days. Each dose of EDTA was dissolved in 500 ml. of aqueous 5 per cent glucose solution and was injected over a one- to three-hour interval. Seven of the patients were women and 2 were Negro. Their average age was 44 years, with a range of 25 to 72 years. Six of them were normotensive, of whom 3 had symptomatic coronary atherosclerosis with anginal attacks, 2 had diabetes mellitus, and the last had nephrosis, clinically, and amyloidosis, pathologically, on the basis of a renal punch biopsy. The remaining 16 patients in the group were characterized by an average supine diastolic hypertension of at least 110 mm. Hg on the basis of a minimum of ten readings in the hospital. Two were in the malignant phase of hypertension characterized by papilledema, exudative and hemorrhagic retinitis, albuminuria, less than 5 per cent excretion of intravenously injected phenol red within fifteen minutes, and a mean diastolic pressure greater than 130 mm. Hg at rest. The rest had less severe hypertension with grade II optic fundi (Keith-Wagener), protein-free urine, and only moderately diminished renal function. No other significant diseases were noted Because of the heterogeneity of the group, individuals are consistently designatec by their disease and a distinguishing number. The nephrotic patient was unique in receiving more than one course of parenteral EDTA; his three courses are chronologically identified by *a*, *b*, and *c*. Any drugs used within the period of observation before, during, and after EDTA administration are indicated in the first pair of tables where the effects of intravenous EDTA on plasma cholesterol and blood pressure are recorded.† In this exploratory study, all the desired laboratory information was not obtained; hence, only the tabulation of reactions to EDTA includes every patient; however, no available pertinent data were excluded. Rectal temperatures and supine blood pressures were measured five or six times a day by qualified nurses on all patients throughout their hospital stay. In 15 patients, total fasting plasma cholesterol levels were determined by the Shoenheimer-Sperry method before and after EDTA.‡

*No form of EDTA except the calcium disodium salt was given either orally or parenterally to any patient considered in this paper. The drug used was generously supplied by Riker Laboratories, Inc., Los Angeles, Calif.

†The atherosclerotic and nephrotic patients were receiving no medication, and the diabetic patients were taking insulin. One-half of the 16 hypertensive patients had been treated with oral hydralazine and/or autonomic blocking agents for at least one year before EDTA was given. Six had received both drugs according to the regimen previously described,[13] and one each had taken hexamethonium chloride and hydralazine alone. All except the last were asymptomatic and controlled with mean diastolic pressures of 100 mm. Hg or less. Their weekly dosages of drugs were relatively constant, varying by an average of 11 per cent. Of the remaining 8 hypertensive patients, 3 received no antihypertensive medication; the other 5, including the pair with malignant hypertension, began hydralazine and ganglionic-blocking agents at approximately the same time as EDTA.

‡Throughout the paper, cholesterol measurements refer to total fasting plasma cholesterol concentrations; all were done in the same laboratory by the same method with the limits of normal lying between 180 and 240 mg. per 100 ml. plasma. The control determinations prior to intravenous EDTA were made within twenty-four hours of the time a patient entered the hospital. In eight instances, a second determination was made after a week of hospitalization and before the addition of any drugs to the prehospital regimen; there were no changes as large as 20 mg. and the average change was an increase of 5 mg. per 100 ml. of plasma. None of the patients changed his diet during the time he received EDTA, and whatever medications he took or toxic reactions he had are indicated in Table I and in the text. The mean weight of the 12 patients without any symptomatic evidence of toxicity varied less than 1 pound during the course of parenteral EDTA, and no single individual weight changed more than 3 pounds.

TABLE I. CHOLESTEROL RESPONSE TO INTRAVENOUS EDTA*

PATIENT	TOTAL FASTING PLASMA CHOLESTEROL LEVELS			MAXIMUM CHANGE FROM PRE-EDTA LEVEL		MEDICATION RECEIVED		
	IMMEDIATE PRE-HYDRALAZINE CHOLESTEROL (MG. %)	IMMEDIATE PRE-EDTA CHOLESTEROL (MG. %)	IMMEDIATE POST-EDTA CHOLESTEROL (MG. %)	1ST WEEK POST-EDTA (MG. %)	2ND THROUGH 8TH WEEK POST-EDTA (MG. %)	DAILY ORAL HYDRALAZINE (GM.)	TOTAL INTRAVENOUS EDTA (GM.)	COURSE OF INTRAVENOUS EDTA (DAYS)
Nephrosis a		518	412	−106	+138	0	16	8
Nephrosis c		537	410	−127	+ 12	0	10	3
Diabetes 1		212	149	− 63	− 20	0	21	8
Hypertension 1		207	136	− 71	——	0	21	7
Hypertension 2		205	168	− 37	+ 48	0	27	11
Diabetes 2		193	139	− 54	+ 2	0	13	5
		204	148	− 55	+ 10		21	
Hypertension 3	211	206	127	− 79	+ 6	0.20	19	8
Hypertension 4	203	184	131	− 51	+ 6	0.50	19	8
Hypertension 5	189	178	127	− 51	− 20	0.50	8	4
Hypertension 6	191	137	121	− 16	——	0.50	3	3
Hypertension 7	214	129	135	+ 6	− 3	0.50	21	7
	202	167	128	− 38	− 1		14	
Hypertension 8		212	——	——	− 57	0.02	10	2
Hypertension 9		205	——	——	− 37	0.40	15	3
Hypertension 10		197	——	——	− 29	0.25	3	1
Hypertension 11		180	140	− 40	− 43	0.15	4	4
Hypertension 12		179	——	——	− 61	0.35	15	3
		195			− 47		9	

*_Changes in Total Fasting Plasma Cholesterol Following Intravenous EDTA With and Without Oral Hydralazine in 15 Patients._—The first 5 received no hydralazine; the second 5 had all taken a constant oral dose for more than a year; and the last 5 began hydralazine during the experiment. For them, the dosage increased and the figure given is an average. The only other drugs taken were autonomic-blocking agents for the second through the sixth hypertensive patients, and insulin for the pair of diabetic subjects. Only the second diabetic, the second hypertensive, and the nephrotic patients had toxic symptoms following EDTA. The latter was unique in receiving more than one course of EDTA; his three courses are indicated chronologically by *a*, *b*, *c*. For better comparison with the rest of the table, the averages in the first part, unlike the text, exclude the hypercholesterolemic nephrotic patient. The pre-hydralazine and pre-EDTA cholesterol levels are identical except for the second quintet where the difference measures the cholesterolytic potency of oral hydralazine therapy.

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The 10 patients who received 1 Gm. daily of oral EDTA are discussed briefly, with the sole objective of indicating the trend of any short-term changes in total plasma cholesterol levels. None of these patients was Negro. Four had benign hypertension as previously defined, four had angina pectoris, one had peripheral vascular disease, and one was convalescing from an occlusion of a coronary artery. None was receiving a special diet or drugs. An eleventh patient, who received only oral EDTA, is mentioned to demonstrate vasoactivity of the compound. No cholesterol data were obtained, but her peculiar blood pressure response is graphed.

Only the cholesterol studies are reported here for the 112 hypertensive patients who received hexamethonium chloride in addition to an average of 0.51 Gm. (range 0.2 to 1.2 Gm.) of oral hydralazine according to a previously described regimen.[13] The hypotensive[13,14] and toxic[15,16] effects of these drugs have been treated elsewhere. The patients were taken consecutively, with the only omissions being those who had additional medication, special diets, reactions to therapy including nausea or significant weight loss, or obvious disease beyond hypertension and its renal, cardiac, and vascular complications. Total plasma cholesterol levels were measured before hydralazine was begun and after varying periods of continuous oral therapy.*

RESULTS

Cholesterol.—The individual changes in total fasting plasma cholesterol for 15 patients before and after intravenous EDTA are recorded in Table I. Within a week of the last injection of EDTA, the mean fall was 75 mg. (55 mg. excluding the nephrotic man) per 100 ml. plasma for the 5 patients who received an average of 18 Gm. of EDTA without other metal binding agent, and 38 mg. for the 5 who received an average of 14 Gm. of EDTA after long stabilization on a constant dose of hydralazine. The minimum cholesterol level was below 150 mg. for 8 of the 10 patients, the two exceptions being the pair who developed mucocutaneous lesions and other signs suggesting vitamin deficiency.[17] Figs. 1 and 2 illustrate the relationship between the daily cholesterol values and the intravenous administration of EDTA in the nephrotic and the second diabetic patient, respectively. The rebound phenomenon following the first course of EDTA in the former also occurred in the first diabetic subject. Hydralazine may have blocked it for the patients in the final two parts of the first table.

Blood Pressure.—Excluding the nephrotic patient and 2 others begun on antihypertensive therapy during intravenous EDTA administration, as well as

*Control pre-hydralazine cholesterol levels were all obtained in the hospital within twenty-four hours of admission, and were preceded by no unusual dietary events. In eighteen instances, individuals in the group had cholesterol determinations made in the outpatient clinics less than three months prior to the control measurement in the hospital. The mean change was a fall of 7 mg. with a standard deviation of 16 mg. per 100 ml. of plasma. In twenty-three instances, members of the group had a pair of cholesterol determinations made in the hospital, the first being within twenty-four hours of admission and the second from seven to ten days later but before hydralazine was begun. The mean change was an increase of 4 mg. with a standard deviation of 12 mg. per 100 ml. of plasma. For the dozen follow-up post-hydralazine determinations which were made during the first ten days of therapy, the patient was eating the regular hospital diet. Twenty-one of the other follow-up determinations were similar to the control values in that they were within twenty-four hours of re-entry to the hospital. The remaining 79 were obtained from outpatients who were consuming their usual diets at home.

5 who received chelator before an adequate control value was obtained, the mean changes in blood pressures of 14 individuals are included in Table II. Of 10 benign hypertensive patients considered in the first part, the blood pressures of the three previously untreated ones fell 17/14 mm. Hg on the average. For the 6 receiving oral ganglionic-blocking agents, the dosage requirement was reduced an average of one-third despite a diminution in mean blood pressure of 9/6 mm. Hg.* The tenth patient, who had no obvious effect from EDTA,

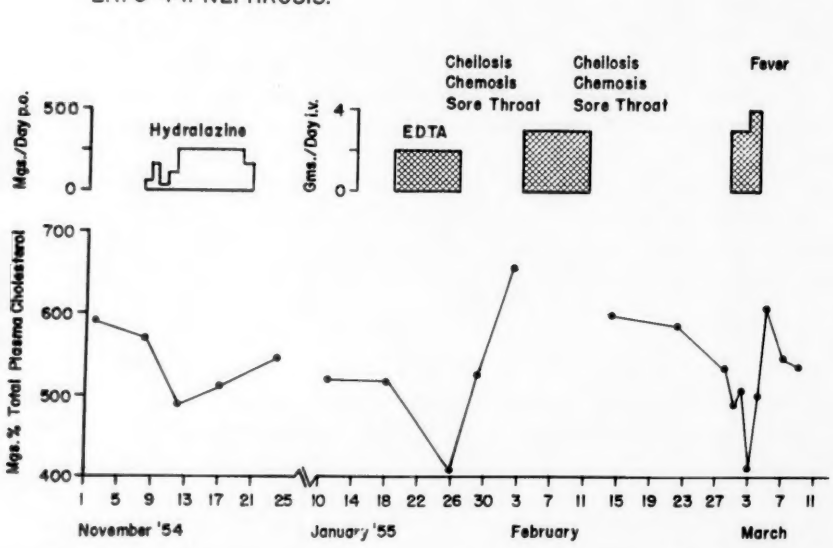

Fig. 1.—Effects of oral hydralazine and intravenous EDTA on plasma cholesterol levels. L. T., 44 years of age, was seen in October, 1954, because of mild exertional dyspnea and ankle edema for six months. At 7 years of age he had Marie-Strumpell arthritis, and at 25 years of age, migratory polyarthritis without urinary symptoms. Nephrosis was clinically evident, and amyloidosis was proved by renal punch biopsy. To lower his plasma cholesterol, hydralazine was begun without evident clinical improvement. In January, 1955, ACTH therapy was followed by hematemesis, melena, and roentgenologic diagnosis of active duodenal ulcer. In a further effort to lower his plasma cholesterol, three courses of parenteral EDTA were given. On the sixth day of this first course of therapy, slight inflammation of the mucous membranes and a magenta tongue were observed, and he complained of soreness about his mouth and gums. By the final day, cheilosis, chemosis, scrotal inflammation, and pustular lesions over the face and trunk had appeared. Within a week, the lesions had vanished and a second course of EDTA was begun. On the fourth day, stomatitis reappeared and within seven days the same syndrome was present again necessitating the discontinuation of therapy. The three-day final course produced no such lesions; however, fever immediately followed the dosage increase to 4 Gm. cholesterol values for the second course were not plotted because such a low plasma level was attained that a laboratory error was suspected (303 mg. per 100 ml. on a single determination). The changes in cholesterol preceded clinical toxicity.

*A change in the requirement for ganglionic-blocking agent can suggest vasoactivity of a second drug. An adequate test system is the patient whose blood pressure is controlled at relatively constant normal levels by a variable intake of blocking agent at four-hour intervals. Ordinarily, such a patient takes a full dose of blocking agent when his systolic pressure exceeds 140 mm. Hg, one-half dose when his pressure is between 140 and 130 mm., one-quarter dose when it is between 130 and 120 mm., and none when it falls below 120 mm. The patients considered here took simultaneous but fixed amounts of hydralazine and the variation in their weekly requirement for blocking agent was small. Therefore, an automatic reduction in dosage without an increase in blood pressure suggests a depressor effect of the additional agent in a patient with well-controlled hypertension. In the presence of moderate hypertension, a decrease of blood pressure with little or no change in blocking agent may indicate the same thing. By considering both blood pressure and dosage of blocking agent, a better evaluation of the vasoactivity of a drug can be obtained.

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never tolerated ganglionic-blocking agents and was inadequately controlled on oral hydralazine alone. The pair of malignant hypertensive patients who make up the second part of Table II had no apparent response to parenteral EDTA.

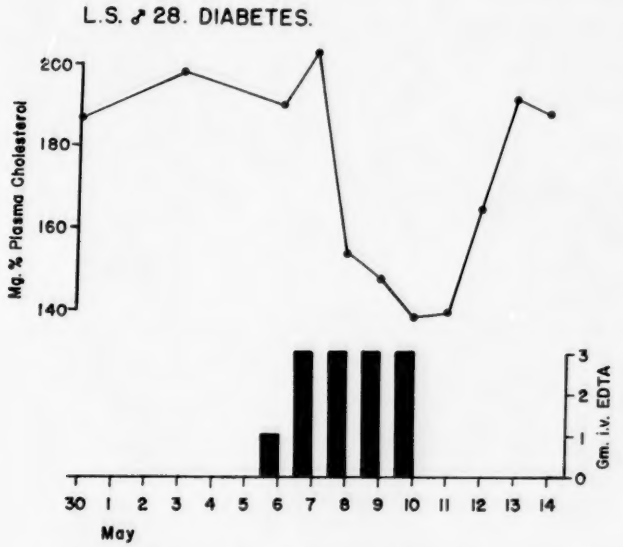
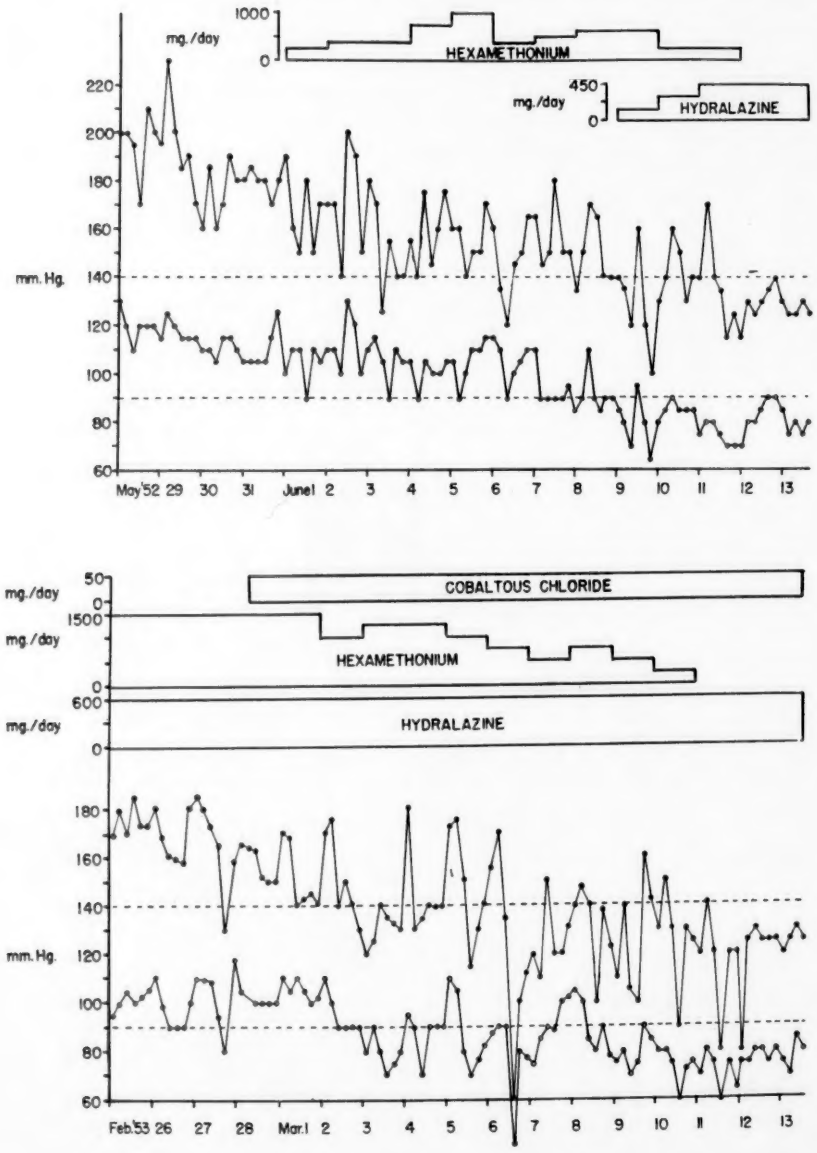


Fig. 2.—Effect of intravenous EDTA on plasma cholesterol.

TABLE II. MEAN BLOOD PRESSURE RESPONSE TO INTRAVENOUS EDTA

PATIENT	MEAN CONTROL BLOOD PRESSURE (MM. HG)	TOTAL EDTA (GM.)	MEAN CHANGE IN BLOOD PRESSURE (MM. HG)	MEAN CHANGE IN METHONIUM (PER CENT)	LONG-STANDING MAINTENANCE THERAPY
Hypertension 8	179/120	10	−22/−19		—
Hypertension 13	194/110	5	−16/−12		—
Hypertension 14	191/129	5	−12/−10		—
Hypertension 3	164/99	19	−21/−12	−33	C_6 and hydralazine
Hypertension 15	145/92	5	−12/−12	−40	C_6 and hydralazine
Hypertension 6	140/83	20	− 5/− 2	−52	C_6 and hydralazine
Hypertension 16	157/100	5	− 4/− 7	−36	C_5 and hydralazine
Hypertension 5	152/93	8	− 1/− 1	−22	C_5 and hydralazine
Hypertension 2	168/82	27	− 8/− 3	−22	C_5
Hypertension 7	183/123	27	+ 6/− 6		Hydralazine
Mean	167/103	13	−10/− 8	−34.2	
Hypertension 9	218/132	15	− 1/+ 3		—
Hypertension 12	196/135	15	+ 3/− 5		—
Diabetes 1	143/79	21	− 7/− 1		Insulin
Diabetes 2	147/86	13	+13/+ 5		Insulin

C_6 indicates oral hexamethonium chloride; C_5, oral pentolinium tartrate. Hydralazine was given orally. Each blood pressure level, or change therein, is the mean of all measurements made either before therapy (average 23, range 12-41) or during the period when the drug was being given (average 19, range 11-36). The mean decrease in methonium intake indicates the lessened requirement for ganglionic blockade to achieve the blood pressure indicated. Each change in medication is based on exactly the same number of recordings as the corresponding change in blood pressure.



A.

Fig. 3,*A*.—*(For legend see opposite page.)*

Both later required large amounts of oral hydralazine and autonomic-blocking agents for satisfactory control. Intravenous EDTA raised both systolic and diastolic pressures slightly in one of the two normotensive diabetic patients who conclude the table. Fig. 3 illustrates a more definite hypertensive effect in the unusual situation of normotension induced by cobalt[6]; however, in this instance the EDTA was given orally.

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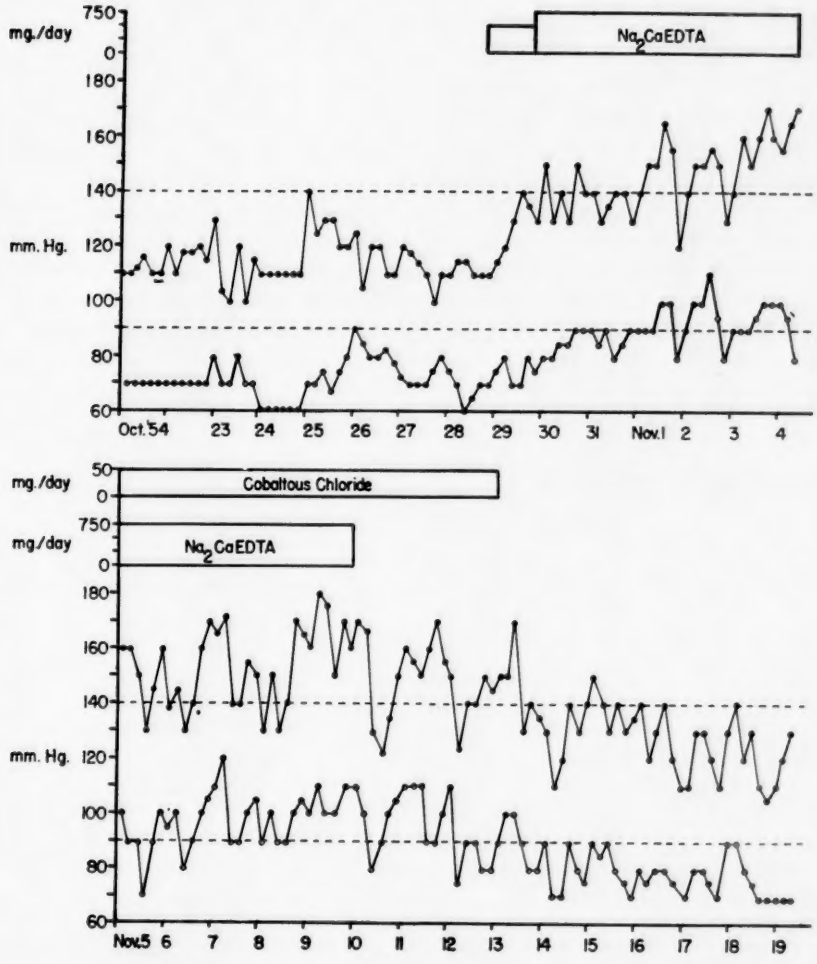

B.

Fig. 3.—Effect of oral cobaltous chloride and oral EDTA on blood pressure. H. D. was a 48-year-old woman with atherosclerotic cerebral vascular damage and hypertension. *A*, These two graphs represent her first two hospitalizations. Control of hypertension was achieved with hexamethonium chloride and hydralazine in May, 1952. Following discharge the patient was not seen until February, 1953; by then her hypertension had become re-established following irregular self-administration of her medication. Within ten days of beginning cobaltous chloride, normal blood pressure was observed despite the automatic elimination of hexamethonium intake. Moreover, normotension continued at home without any drugs. *B*, This pair of graphs represents the third hospitalization. Her blood pressure, which was normal on readmission in October, 1954, rose after EDTA and then returned to normal levels after the addition of cobalt and later the elimination of EDTA. All medication was oral and all blood pressure measurements were made with the patient supine. Except for a period of strict normotension from Oct. 13 to 21, 1954, all sphygmomanometric readings are shown.

Reactions.—Twelve grams of EDTA in 500 ml. of fluid were given to the first atherosclerotic patient in error; syncope resulted within a few minutes of venipuncture, causing the medication to be temporarily discontinued. Later, the remainder was taken at a slower rate without further obvious difficulty, although a brief bout of fever was noted several hours afterward. Eleven of the 22 patients given parenteral EDTA developed similar pyrexic responses without other apparent cause. As indicated in Table III, an elevated temperature occurred after one to three injections in 8 of the 9 individuals who received 4 Gm. or more of intravenous EDTA at a single dose, but in only one of the 13 who received smaller maximum doses. In the one instance where the infusion was repeated twenty-four hours after such a reaction, the second pyrogenic response was almost double the first. The fever was maximal from three to six hours after the medication was begun. Most patients had reachieved normal temperatures twelve hours later, and the rest within twenty-four hours. No evidence of infection could be found, and there were no associated symptoms, signs, or laboratory abnormalities.

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TABLE III. REACTIONS TO INTRAVENOUS EDTA

PATIENT	MAXIMUM SINGLE DOSE (GM.)	TOTAL DOSE (GM./KG.)	NUMBER OF INFUSIONS	MAXIMUM RISE IN TEMPERATURE AFTER LAST INFUSION (DEGREES C.)	COMMENT
Atherosclerosis 1	12	<0.20	1	1.6	Syncope
Hypertension 8	5	<0.20	1	1.5	First infusion
	5	<0.20	2	2.7	Second infusion
Hypertension 13	5	<0.20	1	1.9	
Hypertension 15	5	<0.20	1	1.8	
Hypertension 16	5	<0.20	1	0.6	Shaking chill
Hypertension 9	5	0.23	3	2.2	
Hypertension 12	5	0.25	3	0.6	Shaking chill
Hypertension 14	5	<0.20	1	0	
Nephrosis c	4	<0.20	3	1.5	
Hypertension 10	3	<0.20	1	2.0	
Atherosclerosis 2	3	<0.20	1	0	
Diabetes 2	3	<0.20	5	0	Nausea
Hypertension 3	3	0.22	7	0	
Hypertension 6	3	0.24	8	0	
Hypertension 1	3	0.24	7	0	
Hypertension 4	3	0.24	7	0	
Diabetes 1	3	0.25	8	0	
Nephrosis b	3	0.32	7	0	Mucocutaneous lesions
Hypertension 7	3	0.35	9	1.3	
Hypertension 2	3	0.54	10	0	Mucocutaneous lesions
Hypertension 5	2	<0.20	4	0	
Atherosclerosis 3	2	<0.20	5	0	
Nephrosis a	2	0.24	8	1.4	Mucocutaneous lesions
Hypertension 11	1	<0.20	4	0	

In contrast to the foregoing acute febrile reaction following a single large injection of EDTA, the second hypertensive patient and the nephrotic patient developed a different reaction after ten and eight infusions of smaller amounts

resulting in total doses of 0.54 and 0.24 Gm. per kilogram of body weight, respectively. This delayed reaction was characterized by magenta tongue, sore mouth, cheilosis, chemosis, papular rash, ulceration of buccal mucous membrane,

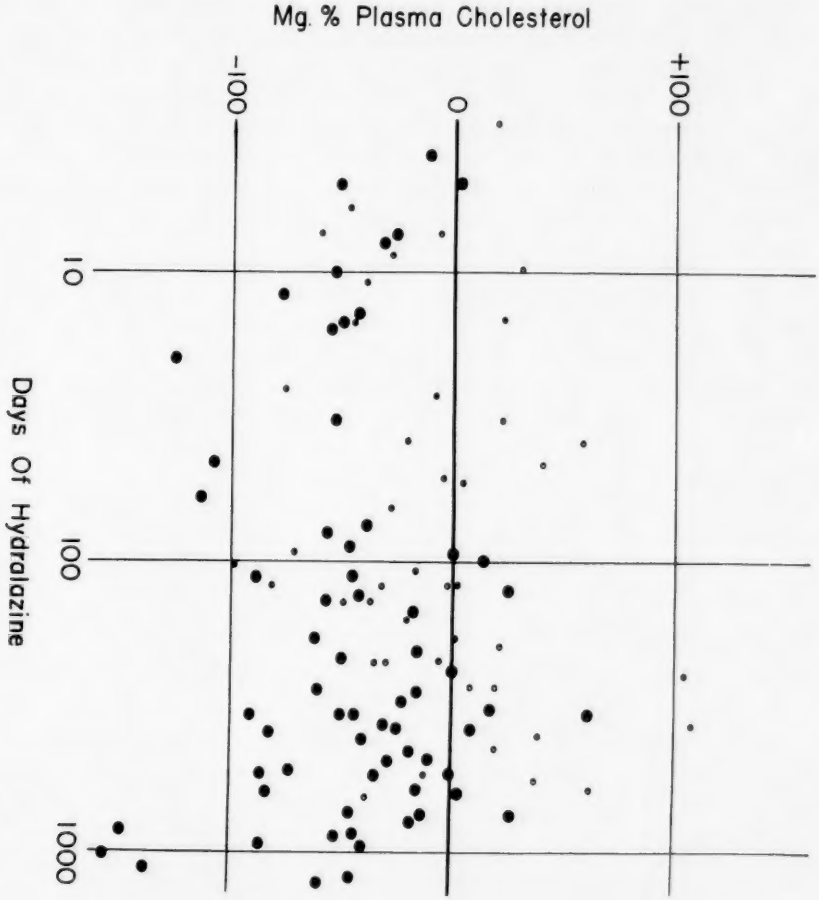

Fig. 4.—Effect of oral hydralazine on total fasting plasma cholesterol in 112 hypertensive patients. Changes in cholesterol concentrations before and after hydralazine are plotted against the length of therapy. Each large dot indicates a patient with an initial cholesterol level of more than 215 mg. per 100 ml. plasma. Each small circle indicates a patient with lower initial values below 211 mg. per 100 ml. plasma.

and, in the case of the nephrotic patient, persistent fever, resembling avitaminosis B. In this patient, trace metal analysis of the urine revealed a fivefold increase in zinc excretion during the third course of EDTA.[17] The seventh hypertensive patient also developed fever which lasted several days after a total dose of 0.35 Gm. of EDTA per kilogram of body weight. Similar, but much milder, reactions of the delayed type may have occurred in the second diabetic patient and in the patient represented in Fig. 3.

Effect of Oral EDTA on Cholesterol.—In Table IV are shown the changes in total fasting plasma cholesterol concentration following 1 Gm. daily of oral calcium disodium EDTA in 10 patients whose diagnoses are indicated. All alterations were initially downward; depressions of 40 mg. per 100 ml. occurred in only one-half. The most marked fall occurred in the first patient mentioned in the table, who had intermittent claudication. Prior to oral EDTA a pair of control cholesterol determinations averaged 278 per 100 ml. plasma. After sixty-four days his level was 145 mg., and after ninety-two days it was 128 mg. per 100 ml. plasma. During chelate therapy, his exercise tolerance improved and his oscillometric readings in both legs increased from 0 to 2 mm. Hg. The 4 patients with severe angina pectoris claimed symptomatic improvement. The initial fall was sustained in only 2 cases.

Effect of Oral Hydralazine on Cholesterol.—In Fig. 4, changes in the total fasting plasma cholesterol concentration are plotted against the length of oral hydralazine therapy for 112 hypertensive patients. The mean fall for the entire group was 29 mg. per 100 ml. of plasma. Of 66 whose initial cholesterol levels were between 216 and 377 mg. per 100 ml. plasma (average 259 mg.), 28 with less than 180 days of hydralazine therapy had a mean decrease of 48.2 ± 4.8 mg. from their control values; while for 38 the mean decrease was 43.5 ± 6.4 mg. after one-half to three and one-half years of treatment.* On the other hand, of 46 patients with initial levels between 215 and 106 mg. per 100 ml. plasma (average 179 mg.), 30 had a mean drop of 17.2 ± 7.2 mg. in the first six months of therapy; whereas 16 had a mean increase of 16.7 ± 13.6 mg. after longer periods of treatment.*

TABLE IV. CHANGE IN PLASMA CHOLESTEROL WITH A DAILY GRAM OF ORAL EDTA

PATIENTS		CONTROL (MG. %)	CHANGE (MG. %)	INTERVAL (WEEKS)	MAJOR DIAGNOSIS
SEX	AGE				
♂	54	278	−150	8	Peripheral vascular disease
♀	70	276	− 40	3	Arterial hypertension
♂	62	253	− 85	16	Coronary occlusion, convalescent
♂	45	252	− 36	31	Angina pectoris
♀	49	237	+ 34	12	Arterial hypertension
♂	77	225	− 74	3	Arterial hypertension
♂	48	210	+ 18	31	Angina pectoris
♂	63	187	− 14	3	Angina pectoris
♂	54	177	− 9	22	Angina pectoris
♀	59	170	+ 14	3	Arterial hypertension

DISCUSSION

Both Table IV and the first part of Table I suggest that the higher the control cholesterol level, the greater the fall following EDTA. Excluding the

*The numbers following the ± are *standard errors* and serve as a measure of the reliability of the means cited. Obviously the first two mean depressions represent a very significant fall in cholesterol; while even the sign of the last one, which indicates an increase in cholesterol, is uncertain.

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markedly hypercholesterolemic patient with nephrosis, intravenous EDTA by itself acutely lowered the mean plasma cholesterol value to 148 mg. per 100 ml. of plasma (Table I) and hydralazine alone, by mouth, chronically lowered it to 167 mg. (Table I). Briefly superimposing parenteral EDTA on continuing oral hydralazine further depressed it to 128 mg. (Table I), suggesting an additive effect. An apparent limit below which metal binding agents will not decrease plasma cholesterol is suggested by the clustering of the concentrations between 121 and 135 mg. after the two agents were used together. If the nephrotic patient is again excluded, the role of pyrogenic reactions in lowering plasma cholesterol levels for the other 9 patients in the first two parts of Table I is demonstrably negligible, since only the seventh hypertensive patient developed fever and he alone showed an increase in cholesterol. Similarly, the delayed reaction characterized by mucocutaneous lesions played no major part since, of the same 9 patients, the only one to develop them had much the highest final cholesterol value. The third part of Table I is less significant, since it is impossible to separate the effect of the EDTA and hydralazine; however, Fig. 4 demonstrates the cholesterolytic response to oral hydralazine in hypertensive patients with higher than average plasma cholesterol levels. Contrary to our initial impression,[6] there is no definite lessening of the effect with time. Obviously, oral EDTA was prolongedly cholesterolytic in only an occasional case.

The mechanism by which a pair of metal binding agents lowers the plasma cholesterol concentration is not clear. Hydralazine is an active compound, the known reactions of which include combination with carbonyl and sulfhydryl groups as well as metal ions.[6] Chemically, however, EDTA is relatively inert; its effects seemingly must be due to chelation of transition or related metals. Hence, if the same mechanism operates in both instances, it is probably mediated by an enzymatic process, the metallic coenzyme for which is affected. The apparent cholesterolytic action recalls the 8-hydroxyquinoline inhibition of hepatic conversion of acetate to cholesterol in the rat rather than the stimulation of that reaction by EDTA.[2] The complicated interrelationships of various metals and binding agents in intact animals may explain diverse actions of chelating agents. In addition, the removal of accumulated "abnormal" elements such as chromium or cadmium, which have been found in human tissues,[18] might be involved. The increased urinary excretion of transition and related metals in untreated "malignant" hypertension[19,20] suggests that the metallic spectra of various organs may be a function of the state of health.

The effect of EDTA on human blood pressure was not comparable to that seen acutely in rats with experimental renal hypertension.[5] The essentially neurogenic basis of the high blood pressure in the patients tested may partly explain the smaller effect observed. The obvious pressor response to oral chelate in one woman is unexplained, but might be considered a reversal of cobalt-induced normotension,[6] since EDTA binds this metal.

Sufficiently large single doses of intravenous EDTA consistently produced brief episodes of fever, a sign also frequently noted in hydralazine toxicity.[16] A different, less acute, and more poorly defined reaction was sometimes eventually produced by repeated infusions of smaller amounts of EDTA. The 2 hyper-

tensive patients who received more EDTA per kilogram of body weight than any other patients developed such delayed reactions. The pair of normotensive patients with similar symptoms had smaller total doses. That toxicity is uncommon when EDTA is used to remove heavy metals may be due to the predilection of the chelator for the poison, thus protecting essential trace metals.

SUMMARY

Twenty-two patients received from 3 to 27 Gm. of intravenous EDTA. Six times after an average total dose of 18 Gm., and without change in other metal binding drugs, the total fasting plasma cholesterol fell an average of 75 mg. per 100 ml. of plasma. Initially low values were altered less. The average depression in 112 unselected hypertensive patients was 29 mg. following oral hydralazine therapy; however, among the 66 with high control levels the fall was 48.2 mg. in the first six months, and thereafter 43.5 mg. per 100 ml. of plasma. In 10 hypertensive patients who received an average of 13 Gm. of EDTA the blood pressure decreased an equivocal 10/8 mm. Hg, although for 6 who took autonomic-blocking agents there was a simultaneous reduction of 34 per cent in the requirement for that drug. Of 9 patients who received single doses of 4 Gm. or more of EDTA, 8 quickly developed fever, and in 2 who received large total doses in relation to their body weight, mucocutaneous lesions were observed.

REFERENCES

1. Curran, G. L.: Effect of Certain Transition Group Elements on Hepatic Synthesis of Cholesterol in the Rat, J. Biol. Chem. **210**:765, 1954.
2. Curran, G. L.: Metal Chelating Agents and Hepatic Cholesterol Synthesis, Proc. Soc. Exper. Biol. & Med. **88**:101, 1955.
3. Rubin, Martin, Martell, Arthur E., and Bersworth, Frederick C.: The Biological Actions of the Versenes, Framingham, Mass., 1954, Versenes, Inc.
4. Uhl, H. S. M., Brown, H. H., Zlathis, A., Zack, B., Myers, G. B., and Boyle, A. J.: Effect of Ethylenediamine Tetraacetic Acid on Cholesterol Metabolism in Rabbits. Preliminary Report on Effect of Parenteral and Oral Administration of Disodium and Calcium Salts, Am. J. Clin. Path. **23**:1226, 1953.
5. Schroeder, H. A., Menhard, E. M., and Perry, H. M., Jr.: Antihypertensive Effects of Metal Binding Agents, J. Lab. & Clin. Med. **46**:416, 1955.
6. Perry, H. M., Jr., and Schroeder, H. A.: Studies on the Control of Hypertension by Hyphex. III. Pharmacological and Chemical Observations on 1-Hydrazinophthalazine, Am. J. M. Sc. **228**:396, 1954.
7. Pauli, W.: Ueber Ionenwirkungen und ihre therapeutische Verwendung, München. med. Wchnschr. **50**:153, 1903.
8. Page, I. H., Corcoran, A. C., Dustan, H. P., and Koppanyi, T.: Cardiovascular Actions of Sodium Nitroprusside in Animals and Hypertensive Patients, Circulation **11**:188, 1955.
9. Black, M. M., Zweifach, B. W., and Speer, F. D.: Comparison of Hypotensive Action of Sodium Azide in Normotensive and Hypertensive Patients, Proc. Soc. Exper. Biol. & Med. **85**:11, 1954.
10. Schroeder, H. A.: The Antihypertensive Influence of Certain Sulfhydryl Compounds, Science **114**:441, 1951.
11. Schroeder, H. A., Menhard, E. M., and Perry, H. M., Jr.: The Antihypertensive Properties of Some Mercaptans and Other Sulfur-containing Compounds, J. Lab. & Clin. Med. **45**:431, 1955.
12. Perry, H. M., Jr., Teitelbaum, S., and Schwartz, P. L.: Effects of Antihypertensive Agents on Amino Acid Decarboxylation and Amine Oxidation, Federation Proc. **14**:113, 1955.
13. Schroeder, H. A., Morrow, J. D., and Perry, H. M., Jr.: Studies on the Control of Hypertension by Hyphex. I. Effect on Blood Pressure, Circulation **8**:672, 1953.
14. Perry, H. M., Jr., and Schroeder, H. A.: Studies on the Control of Hypertension by Hyphex. VI. Some Evidence for Reversal of the Process, (Submitted for publication.)

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15. Morrow, J. D., Schroeder, H. A., and Perry, H. M., Jr.: Studies on the Control of Hypertension by Hyphex. II. Toxic Reactions and Side Effects, Circulation **8**:829, 1953.
16. Perry, H. M., Jr., and Schroeder, H. A.: Syndrome Simulating Collagen Disease Caused by Hydralazine (Apresoline), J. A. M. A. **154**:670, 1954.
17. Schroeder, H. A., and Perry, H. M., Jr.: Lesions Resembling Vitamin B Complex Deficiency and Urinary Loss of Zinc Produced by Ethylenediamine Tetraacetate, (To be published.)
18. Tipton, I. H., Steiner, R. L., Foland, W. D., Mueller, J., and Stanley, M.: Spectrographic Analysis of the Tissues from Autopsies of Twenty-four Instantaneous Deaths, Oak Ridge National Laboratory Report, C. F. 54-12-66, Dec. 10, 1954.
19. Perry, H. M., Jr., Schroeder, H. A., and Frederickson, A. F.: Urinary Trace Metals From Normal and Treated and Untreated Hypertensive Patients, J. Lab. & Clin. Med. **44**:907, 1954.
20. Perry, H. M., Jr., and Schroeder, H. A.: A Comparison of the Concentration of Several Trace Metals in the Urine of Treated and Untreated Malignant Hypertensive Patients as Compared With Normal Individuals, to be presented to the Central Society For Clinical Investigation, Nov. 1955 (abstract, in press).

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SOME EXPERIENCES WITH PHYSICAL DISABILITIES FROM CHRONIC ILLNESS IN OLD PERSONS

AUSTIN B. CHINN, M.D., AND RUTH MASON, M.S.

CLEVELAND, OHIO

From the Department of Medicine, Western Reserve University School of Medicine and Benjamin Rose Hospital

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A HOSPITAL, recently established in Cleveland for the management of long-term illness in older people, has provided an opportunity for making observations of various influences of these illnesses with respect to the individual, the family, and the community. This communication is concerned solely with the nature of the physical disabilities and results of physical rehabilitative efforts in an initial group of patients admitted to this hospital. Obviously, the physical aspects of long-term illness represent only a portion of each patient's total health problem, and, in a future communication, pertinent psychiatric, social, and economic aspects will be discussed. Though it cannot be said that the physical side of long-term illness is more or less important than other aspects, it is usually the factor which brings concerted attention to the individual patient. Because we have dealt with serious incapacitating sickness in a group of very old people and have been encouraged by this early experience, it is believed worthy of comment.

CASE MATERIAL

Certain observations concerned with the physical disabilities of the first 100 persons admitted to the Benjamin Rose Hospital will be described in the present report. Except for the fact that they did not present problems for obvious custodial or domiciliary care, these persons represented an unselected group, and were uniform only in that, because of their illnesses, they were thought to need either hospital evaluation, treatment, or both. The duration of hospitalization varied from two weeks to seven months, with an average stay of just under two months. Those patients who, it was thought, could benefit by physical rehabilitative treatment, received intensive physical therapy with muscular training and instruction in daily living activities, in addition to indicated medical and surgical measures. Among the first 100 persons admitted, 14 died during the initial hospitalization, leaving 86 who were discharged. Since we are concerned here with experiences and results from hospital management, information about the 86 persons who survived hospitalization is all that is considered pertinent.

OBSERVATIONS

Fig. 1 represents the age grouping of the 86 persons at the time of hospital admission. The average age was 77 years. Table I gives a listing with incidence of the major physical diseases in these patients. Although most of them had multiple disease states, only the principal incapacitating illnesses are listed.

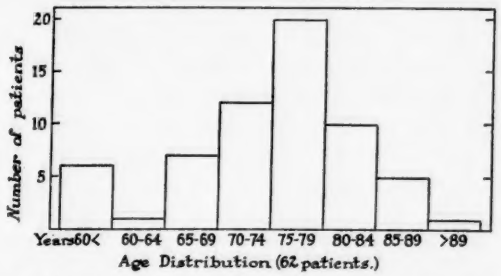

Fig. 1.—Distribution of age groups in 86 patients admitted to and discharged from hospital.

TABLE I. INCAPACITATING ILLNESSES IN 86 PATIENTS ADMITTED TO AND DISCHARGED FROM HOSPITAL

DIAGNOSIS	NUMBER
1. None	0
2. Cerebral vascular accident	26
3. Cerebral arteriosclerosis	13
4. Parkinson's disease	4
5. Hypertensive cardiovascular disease	34
6. Arteriosclerotic heart disease	13
7. Fractures	19
8. Rheumatoid arthritis	5
9. Osteoarthritis	13
10. Diabetes	7
11. Malnutrition and general debility	6
12. Obesity	3
13. Decubitus ulcers	4
14. Convalescent care	2
15. Malignant tumors	7
16. System disease other than above	
a. Skin	3
b. Cardiac	0
c. Pulmonary	5
d. G-I	6
e. Renal	5
f. Lower G-U tract	5
g. Hematological	2
h. Skeletal	0
i. C N S	3
j. Endocrine	0
k. Eyes, ears	2

Such conditions as osteoporosis, emphysema, lower urinary tract infections, hypertension, etc., when not incapacitating and therefore not a cause per se of hospitalization, have not been listed. It should suffice to say that the medical and surgical management of these various illnesses was in accord with the standards of good practice.

The practical results of hospitalization of the patients is believed to be best illustrated through a description of their functional capacities for daily living. Seven basic functions were selected as best representing the physical capabilities of the whole patient and each patient was analyzed for these at the time of hospital admission and at the time of discharge. Fig. 2 represents the distribution of these seven basic functional capacities in the 86 patients at the time of hospital admission and discharge. It should be remembered that this figure includes not only the patients who were given physical rehabilitative treatment, but also those who, after evaluation, were believed not capable of benefiting from treatment. Despite this fact, the information would seem to indicate that, in the group as a whole, there was appreciable improvement in most of the daily living requirements at the end of their hospital stay, even though the duration of restricted physical capacities had been in existence for weeks in almost all patients, and for months in some, previous to hospital admission.

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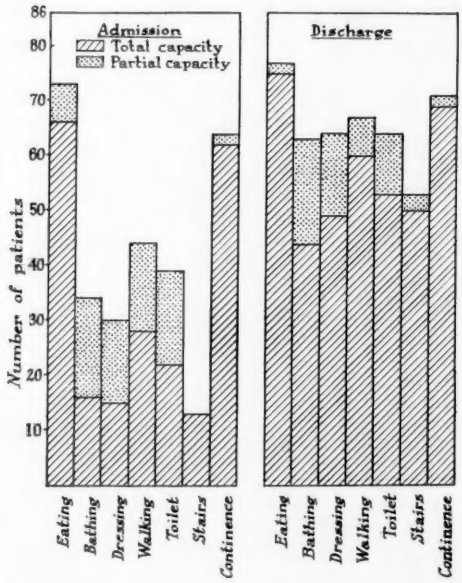

Fig. 2.—Distribution of seven functional capacities in 86 patients at time of hospital admission and discharge.

In order more fully to appreciate the comparable status of the individual patient at the time of admission and discharge, an attempt has been made to identify each by a numerical figure. To each of the already described functional capacities has been attached an arbitrary figure which has been varied according to what was thought to be the relative psychologic, sociologic, and nursing advantage to the patient who could perform a given function. For instance, the value attached to the function of eating is, logically, less than that attached to bowel and urinary continence. Table II gives the values attached to each of the seven functional capacities, both when performed by the patient alone

TABLE II. NUMERICAL VALUES GIVEN TO SEVEN FUNCTIONAL CAPACITIES WHEN PERFORMED ALONE AND WITH HELP

	FULL CAPACITY VALUE	PARTIAL CAPACITY VALUE
1. Eating	2	1
2. Bathing	4	2
3. Dressing	6	3
4. Walking	8	4
5. Toilet	10	5
6. Stairs	10	5
7. Continence	10	5
Total	50	25

and when performed only with assistance. It is fully appreciated that this is an arbitrary means of expression and is not without error, particularly in the numerical relationship of these capacities to each other. It may be seen that, with this means of expression, any one patient at a given time might have a total numerical value in the range of 0 to 50.

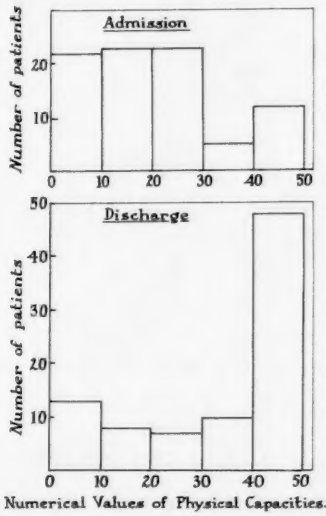

Fig. 3.—Distribution of numerical profiles of 86 patients at time of hospital admission and discharge.

Fig. 3 represents the distribution of these numerical profiles in the 86 patients at the time of admission and discharge. It is quite evident that a substantial number of patients were appreciably more capable of self-care on leaving the hospital than when admitted.

In order to express this, and to show the number of patients who actually did improve and to what extent they improved, Fig. 4 has been made. This represents the distribution of values obtained when the admission numerical value for each patient was subtracted from the discharge value. It is obvious

that during hospitalization a considerable number of patients (23) did not change at all, and that 7 patients actually regressed functionally. On the other hand, 36 patients improved to the extent of increasing their numerical values more than 20 points.

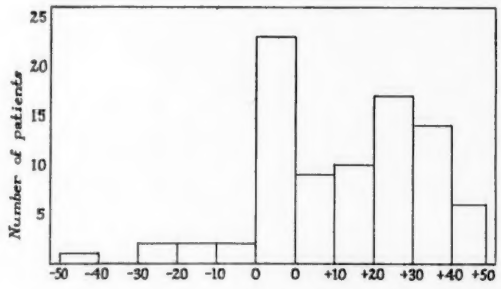

Fig. 4.—Distribution of net numerical values for 86 patients, obtained by subtracting hospital admission values from hospital discharge values.

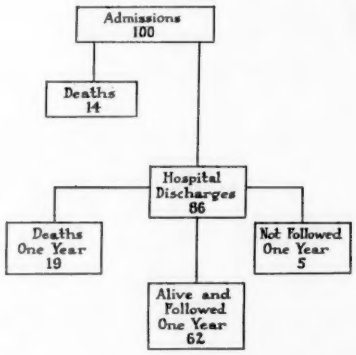

Fig. 5.—Fate of first 100 patients admitted to the hospital.

FOLLOW-UP OBSERVATIONS

Having accumulated the experience already described, it was deemed a worthwhile undertaking to determine the status of each of the 86 patients still living one year after leaving the hospital. Information was therefore collected about each individual's functioning capacities at the year's end. This information was in almost all instances obtained by personal interview and evaluation of each patient by the authors, although, in a few instances, testimony of another reliable observer was taken.

In Fig. 5, the fate of the original 100 patients admitted is outlined. Of the 86 who left the hospital, 19 were dead within one year, and 62 were followed at one year after hospital discharge. Fig. 6 gives the age distribution of these 62 living patients and Table III their incapacitating illnesses at the time they

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were in the hospital. These data compare proportionately to those on the whole group of 86 and would indicate that in so far as age and the nature of illnesses were concerned, no special group of patients survived for one year after hospital discharge.

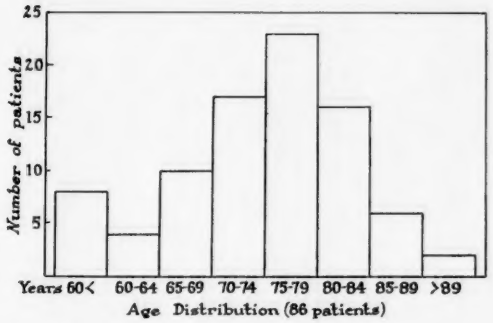

Fig. 6.—Distribution of age groups in 62 patients, followed one year after hospital discharge.

The distribution of the seven basic functions for these 62 patients at the time of hospital admission, hospital discharge, and one year after discharge is presented in Fig. 7. It is quite evident that the increase in these functional activities at the time of hospital discharge was to a large measure preserved in those patients who were living at the end of one year.

TABLE III. INCAPACITATING ILLNESSES IN 62 PATIENTS, FOLLOWED ONE YEAR AFTER HOSPITAL DISCHARGE

DIAGNOSIS	NUMBER
1. None	0
2. Cerebral vascular accident	20
3. Cerebral arteriosclerosis	10
4. Parkinson's disease	3
5. Hypertensive cardiovascular disease	24
6. Arteriosclerotic heart disease	7
7. Fractures	13
8. Rheumatoid arthritis	4
9. Osteoarthritis	10
10. Diabetes	5
11. Malnutrition and general debility	2
12. Obesity	3
13. Decubitus ulcers	1
14. Convalescent care	3
15. Malignant tumors	2
16. System disease other than above	
a. Skin	2
b. Cardiac	0
c. Pulmonary	3
d. G-I	3
e. Renal	2
f. Lower G-U tract	4
g. Hematological	2
h. Skeletal	0
i. C N S	2
j. Endocrine	0
k. Eyes, ears	1

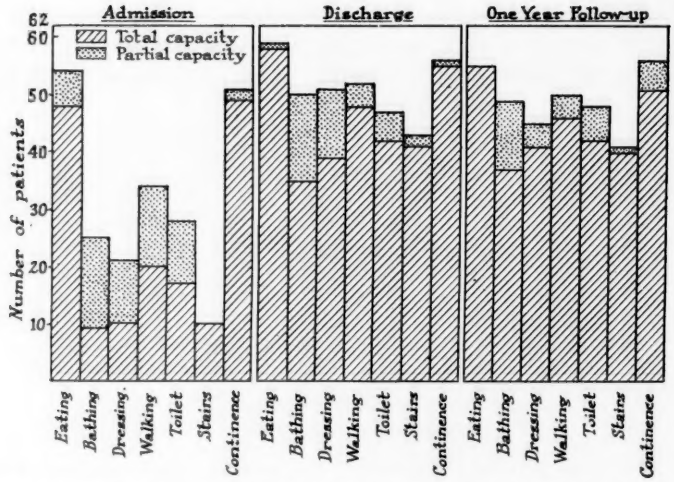

Fig. 7.—Distribution of seven functional capacities in 62 patients at time of hospital admission, discharge, and one year after hospital discharge.

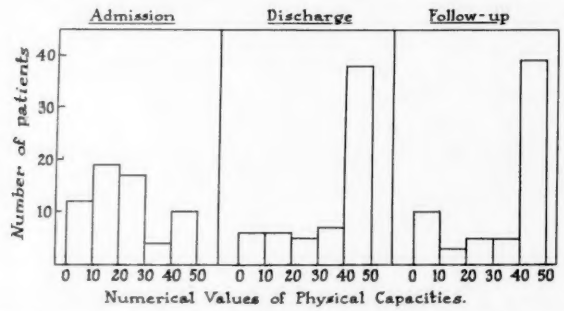

Fig. 8.—Distribution of numerical profiles in 62 patients at time of hospital admission, discharge, and one year after hospital discharge.

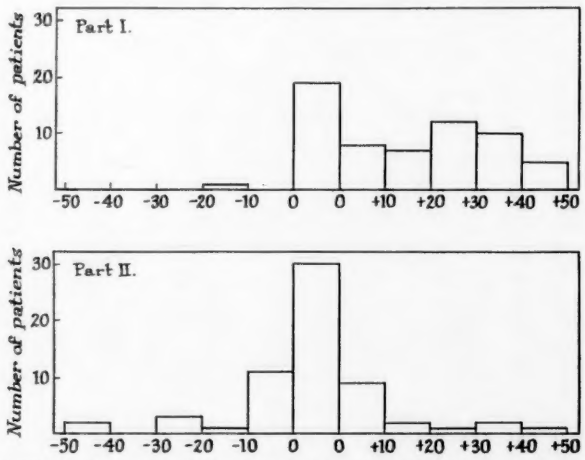

Fig. 9.—Distribution of net numerical values in 62 patients followed one year after hospital discharge. *Part I*, Hospital admission values subtracted from hospital discharge values. *Part II*, Hospital discharge values subtracted from one year follow-up values.

The distribution of numerical profiles for the individual 62 patients at the time of admission, at the time of discharge, and one year later is illustrated in Fig. 8. The increase in functional capacities of individuals during the hospital stay, and their preservation for one year, is again illustrated by this means.

Part I of Fig. 9 illustrates the distribution of the net differences obtained by subtracting admission values from discharge values, and Part II illustrates the distribution of those net differences obtained by subtracting the discharge values from the one year follow-up values. In these 62 people, there was a decided increase in functional capacity in a good many patients during hospital stay; during the year after discharge, most patients who survived remained essentially unchanged.

COMMENT

From the data presented it is evident that, as a group, the 86 aged and chronically ill persons who were admitted and discharged from the hospital achieved significant improvement in their functional capacities and requirements for daily living while in the hospital. The one year follow-up information on the 62 living patients indicates, moreover, that those persons who survived the year after hospital discharge retained the functional improvement acquired while in the hospital. This information, we believe, is important when one considers the traditional aura of hopelessness generally surrounding serious illness in such an aged group of people. The fact that the data are derived from an unselected group of patients adds to its meaning.

It is very difficult to measure the individual and community influence brought about by the physical betterment of any one of these patients. Assuredly, a measure of self-care exhibited by any one has a very substantial social and economic impact. The money and effort invested in the hospitalization of each of these patients appears to have been rewarded, particularly since those that lived as long as a year after hospital discharge did for the most part retain the functional status present at hospital discharge. Despite the fact, therefore, that present experience indicates that out of any 100 such patients admitted to a hospital, roughly one-third will not benefit at all, and about one-third will be dead within a year of hospital discharge, the increased capabilities of those who do improve and survive would appear to justify the undertaking.

Because this was a new hospital with no established precedents, a word with respect to certain experiences in its operation might be of interest. It was the original intention that patients should be admitted who, it was thought, could be particularly benefited by the special facilities and techniques available only in a hospital. It was learned very early, however, that without a period of observation, opinions as to the potential of any one patient for benefiting from hospitalization were in error too frequently to make the plan workable. Some patients with chronic sickness, who, before a period of observation, gave little promise of being benefited, gained a great deal from intensive treatment; occasionally the reverse was true. For these reasons, it is our belief that no common means of measurement can be utilized for all patients and that most aged people with chronic illness, however devastating, deserve to be hospitalized at some time, for proper evaluation and effort at treatment.

A second of the original policies was one relative to the continued hospitalization of patients who were thought to be no longer capable of benefit from specific hospital facilities. In an institution of this character, it is often a temptation to continue the patient in the institution far beyond his actual needs. We believe it economically unsound and professionally wasteful to keep patients in the expensive environment of the hospital when they can live with equal comfort and service elsewhere. This policy has been adhered to, and, generally speaking, has worked so successfully that this hospital of very small capacity has cared for a surprisingly large number of people. The program is greatly dependent upon a vigorous medical social service organization. Each patient has a preliminary social service evaluation before hospital admission with follow-through during and after hospitalization. As a result of these experiences, it is believed that any efficient hospital caring for patients with chronic illness can no more do without proper medical social services than without the facilities for proper medical and nursing care.

At this point it might be well to point out that the acceptance of old people with grave incapacitating illness into any hospital calls for particular attitudes from all personnel surrounding them. It most certainly is true that the maximal benefit to be derived from evaluation and treatment requires of the medical, nursing, and technical personnel attitudes whereby every possible mental and physical resource of the patient is utilized and enlarged upon. Oftentimes, seemingly small gains must be looked upon as major accomplishments. It is only through such attitudes that the morale and service of a hospital may remain high with substantial profit to the patients and the people who work with them.

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SUMMARY AND CONCLUSIONS

1. Certain experiences with the physical disabilities of 100 chronically ill, aged persons, admitted to a hospital for evaluation and/or treatment are described.

2. Approximately one-third of an unselected group of such persons may be substantially improved for their daily living requirements by intensive treatment.

3. Follow-up information indicates that such physical improvement, achieved while in the hospital, is in large measure preserved in those patients who survive for one year after hospital discharge.

4. This sustained physical betterment in the aged person is believed to have a significant socioeconomic influence on the individual, family, and community.

5. Certain other experiences relative to the management of a chronic disease hospital for the aged are described.

UNTREATED SYPHILIS IN THE MALE NEGRO

Background and Current Status of Patients in the Tuskegee Study

Stanley H. Schuman, M.D.,* Sidney Olansky, M.D.,**
Eunice Rivers, R.N.,*** C. A. Smith, M.D.,****
and Dorothy S. Rambo, R.N.*****

From the Venereal Disease Program, Division of Special Health Services, U. S. Public Health Service, Washington, D. C.†

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THIS report is one of a series[1-9] concerning a study of untreated acquired syphilis in the male Negro in Macon County, Alabama, conducted by the Venereal Disease Program, Division of Special Health Services, United States Public Health Service. Previous reports have dealt with: the various abnormalities found in untreated syphilitic individuals and nonsyphilitic controls at the time of the initial examination; the life expectancy of the respective groups after twelve years' observation; the abnormalities among untreated syphilis patients with special attention to the cardiovascular system after six years' observation; and a comparison of physiologic changes in the groups after sixteen years' observation.

HISTORICAL BACKGROUND

The natural history of untreated syphilis, that is, the incidence and types of complications, the occurrence of latency, and the incidence of spontaneous cure in the host, unaided by specific therapy, has been surmised chiefly from the work and reports of Boeck and Bruusgaard in Oslo, Norway. In 1927, Bruusgaard,[10] and, more recently, Gjestland,[11] have sought out and re-examined the survivors of the original members of Boeck's syphilis clinic in which, from

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This article is one of a series on untreated syphilis in the male Negro which the Veneral Disease Program, Division of Special Health Services, plans to assemble into a monograph. Single copies of the monograph will be made available upon request to the Venereal Disease Program, Division of Special Health Services, U. S. Public Health Service, Washington 25, D. C.

*Formerly, Senior Assistant Surgeon, U. S. Public Health Service, Venereal Disease Research Laboratory, Chamblee, Ga. Now in private practice.

**Director, Venereal Disease Research Laboratory.

***Macon County Health Department, Tuskegee, Ala.; Scientific Assistant, Venereal Disease Program.

****Chief, Venereal Disease Program.

*****Statistician, Venereal Disease Research Laboratory.

†With statistical assistance from the Office of Statistics, Venereal Disease Program.

1889 to 1910, mercury, the only drug available, was withheld from the patients as being of questionable value and, perhaps, of harm. This had constituted the only well-studied and documented group of untreated syphilis patients in medical literature.

In 1946, Rosahn[12] published results of a retrospective study of untreated syphilis cases coming to autopsy at Yale University hospitals.

As described in detail by Olansky and associates,[6] the present study arose as an outgrowth of one of the earliest extensive blood-testing and syphilis treatment programs in the United States, sponsored by the Rosenwald Fund and then by the Public Health Service in Macon County, Alabama, in 1930 and 1932, respectively. These surveys revealed a shocking incidence of syphilis which marked the area to be one of "saturation" with the untreated disease. After treatment of the acute cases, a group of Negro men over 25 years of age, who volunteered for the examination, were selected for study. It was agreed that they would be kept under observation by the local health officer and public health nurse; that they would be examined at intervals, to check on their physical status; and they would not be given specific therapy for syphilis, if syphilitic. A group of approximately 400 individuals was selected, in all of whom the diagnosis of syphilis was made in accordance with criteria laid down at the time and detailed elsewhere.[1] A control group, selected to match with respect to age and general social level, was taken from among the nonsyphilitic population examined in the survey, and was considered as nonsyphilitic on the basis of seronegativity and freedom of history or signs of the disease. At the time the groups were selected from a farming community of poor, rural, southern Negroes, the socioeconomic and health status was generally so low that the only difference between syphilitic and control groups was in the presence or absence of evidence of syphilis.

In the fall of 1951, a fourth survey of the survivors of the original study group was begun. An effort was made to locate as many of the men as possible in order to gather maximum clinical and serologic information, as well as to determine whether or not the advent of the "antibiotic era" had defeated the project as a study of untreated syphilitic men. It was anticipated that history taking would be more important, and perhaps more difficult, than previously, in respect to type, amount, date, and source of any treatment received. A special field investigator was assigned to the survey. He helped the nurse follow-up worker in locating and transporting the patients and, also, sought information relating to treatment and socioeconomic status from each patient.

The beginning of this survey coincided with a visit to the United States of Gjestland of Norway, the chief worker in the current re-examination and re-evaluation of the survivors of the Boeck-Bruusgaard study. At the invitation of the Division of Venereal Disease, he visited Tuskegee and observed the first group of patients as they were examined. He saw, first hand, the remarkable socioeconomic and racial difference between the rural Alabama Negro farmers and the fair-skinned Norwegians whom he has been studying.

As the first aged men trooped into the hospital for examination, Dr. Gjestland and the examiners felt as if they were witnessing a strange and historic

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procession. Their feelings were similar to those of Bruusgaard who wrote in 1929, "It produced a curious impression to see these patients after so many years . . . several of them over 70 . . . a strikingly large percent of the cases were free of clinical symptoms . . . many of these patients had apparently tried to undermine their health by an unreasonable mode of life, but had not succeeded. . ."[10]

Despite the similarities, however, certain striking differences between these two studies of untreated syphilis are apparent and are listed in Table I.

TABLE I. TABULAR LISTING OF DIFFERENCES IN THE UNTREATED SYPHILIS STUDIES IN ALABAMA AND IN NORWAY

	ALABAMA	NORWAY
Study population composition	Rural Negro men	White men and women
Control	Nonsyphilitic controls observed	No controls
Percentage autopsied of those who have died	63.3 per cent	24.3 per cent
Patient motivation for study participation	Volunteers with social incentives	Sickness and disability
Treatment status	Small amounts, especially in younger men	Less treatment available, especially in early years of study
Clinical facilities	Newer x-ray, EKG, and serologic techniques	Best medical facilities of the time (1925-1927)
Spinal fluid examination	Most of the syphilitic patients had spinal fluid examinations at start of study	No routine spinal fluid examination reported
Selection of patient material	Acute syphilis and younger patients treated and omitted at start of study; early and late latent patients studied and followed	Only early, untreated syphilis included

METHODS

Many of the techniques used in this survey were based on previous experience, for example, timing. The "slack" season, between fall harvest and spring planting, has been most advantageous for the periodic examinations. The modern Veterans Administration Hospital in Tuskegee was utilized. An experienced public health nurse and follow-up worker contacted the men by letter and home visits.[9] Transporation to and from the hospital was provided. Incentives in the form of free, hot lunches and free medicine (for diseases other than syphilis) were given. One of the chief innovations in the current survey was emphasis on epidemiologic methods of tracing and contacting every possible survivor of the original study group. With the assistance of a trained field investigator, and with the cooperation of Venereal Disease Control officers in distant cities and states, most of the individuals now included in the study group have been traced; 209 of the total group (syphilitic patients and controls) are known to be dead, 332 are known to be living, and 59 are considered lost from observation, although efforts still are being made to trace them. Nine men still living in Macon County did not cooperate during the recent examination. These

men, too, are being observed, although "at a distance"; news of their illness or disability is readily available. A few examinations were made during home visits to farmers who were isolated or apathetic. In several instances, the patient was surprised during his morning plowing and asked to step in the shade of the nearest tree for an on-the-spot history, physical examination, and bloodletting. The survey team, consisting of a physician, nurse, and an interviewer-investigator, worked in Macon County from November, 1951, to June, 1952. Table II shows the number of examinations performed in this recent survey.

TABLE II. DISTRIBUTION OF SYPHILITIC AND NONSYPHILITIC PATIENTS EXAMINED IN THE 1951-1952 SURVEY

	NONSYPHILITIC PATIENTS	SYPHILITIC PATIENTS	TOTAL
Examined in Macon County, Alabama	93	139	232
Examined outside of Macon County	12	21	33
Total examined	105	160	265

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THE STUDY POPULATION

During twenty years of observation, the study population has undergone changes, most significant of which are due to higher mortality rates among the syphilitic individuals. Before such changes can be properly evaluated, the composition of the study group from the beginning of the study should be reviewed. During 1932-1933, 412 syphilitic and 204 nonsyphilitic Negro men were selected for study. During 1938, at the time of the second physical examination, 14 untreated syphilitic individuals were added to the group. Reports on this study population, published during the course of the study, have included varying numbers of syphilitic and nonsyphilitic patients. This has been due to different interpretations by the various clinicians and analysts in regard to the criteria set up for the selection of study patients.

Prior to the preparation of reports based on the results of the 1951-1952 survey of the patients, a complete review of the records was undertaken to determine, as nearly as possible, which patients actually met the study criteria as originally set up and had maintained their original status during the twenty years of observation, 1932 to 1952. Questionable case histories were discussed by two clinicians, a serologist, and a record analyst, all of whom are closely associated with the study. It was determined, as a result of this careful consideration, that six individuals (four in the syphilitic and two in the control group) did not meet the criteria set up for inclusion in the study. These, in addition to the 14 persons who were added to the syphilitic group in 1938 and who, therefore, were under observation for only 14 years, are presently excluded from the syphilitic group. Also excluded are 10 individuals in the original nonsyphilitic group who acquired syphilitic infection at some time during the 1932 to 1952 period of observation.

With these exclusions, the current series of reports is based on the case histories of 408 syphilitic and 192 nonsyphilitic individuals. Of the 408 syphilitic patients, 208 were living, 41 are of unknown status, and 159* were known to be dead at the beginning of the 1951-1952 survey. Of the nonsyphilitic group, 124 were living, 18 were of unknown status, and 50* were known to be dead.

The exclusion of the 18 syphilitic patients and 12 control patients from this series of reports does not mean that care and examination of these latter patients will be discontinued. An attempt will be made, as in the case of the other study patients, to follow these individuals through to autopsy, where findings at that time may prove to be as informative as those for the major study group.

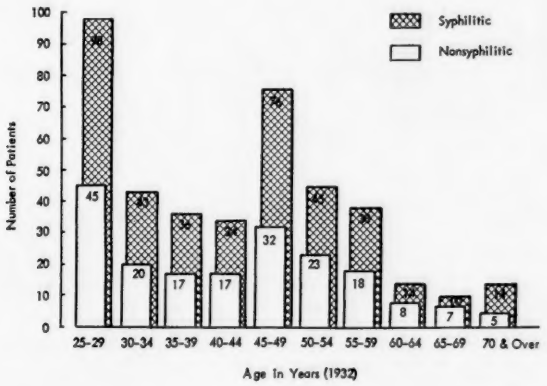

Fig. 1.—Distribution of study population by age in 1932, showing the ratio of syphilitic to nonsyphilitic patients.

AGES

Age grouping is one of the chief classifications used in this and previous reports. Most abnormalities are noted with respect to age group, syphilitic patients being compared to nonsyphilitic controls. The importance of comparable numbers in each age group was recognized at the start of the study.

Shortly after the syphilitic individuals were selected, nonsyphilitic subjects were sought to match them in age distribution according to a fixed ratio. Fig. 1 shows approximately twice as many syphilitic as nonsyphilitic subjects in each age group. The variations from this 2:1 ratio are not due to errors in the selection of the men in 1932, but rather to inconsistent ages given by certain individuals who were uncertain of their age.

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*Six syphilitic patients and one nonsyphilitic patient died during 1952 after having been examined in the 1951-1952 survey. Since physical findings on these individuals have been included among those of the examined group, these patients are, for purposes of this report, considered to be living and examined. In the report on comparative life expectancies[5] of the syphilitic and nonsyphilitic groups, these seven patients have been included among the deaths since the expectancies were based on mortality experience through the year 1952.

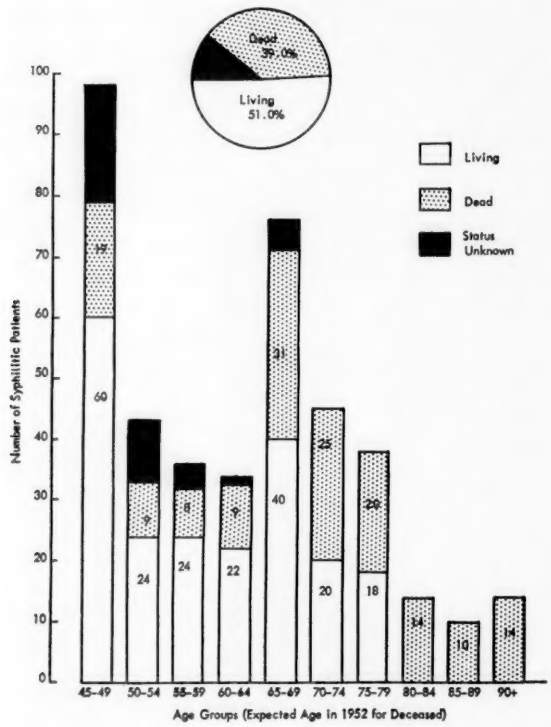

Fig. 2*A*.—Status of syphilitic patients in study population in 1952, considered as a whole and by age groups.

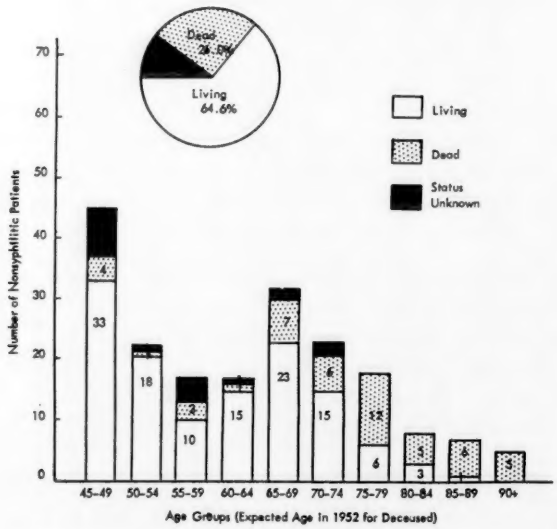

Fig. 2*B*.—Status of nonsyphilitic patients in study population in 1952, considered as a whole and by age groups.

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STATUS OF THE STUDY POPULATION AFTER TWENTY YEARS

In Figs. 2*A* and 2*B*, the syphilitic and nonsyphilitic groups are compared after twenty years of observation. The majority of men lost or lapsed from observation are in the younger age groups; the young being traditionally more mobile than older, settled men. It is fortunate for the study, however, that many of the men who have moved out of Macon County continue to communicate with the public health nurse in Tuskegee or later return to their homesteads. The percentage of men lost from observation is comparable in each group, 10 per cent of the syphilitic patients and 9.4 per cent of the nonsyphilitic subjects. These figures add validity to the findings in the study, not only because they show that relatively few men have been lost from observation, but also because they indicate that interest in the diseased men has not overshadowed the follow-up study of the equally important nonsyphilitic controls.

MORTALITY COMPARED

The relative mortality of syphilitic patients compared to nonsyphilitic controls is shown somewhat differently in Figs. 2*A*, 2*B*, and 3. As all previous workers in this study have found, the most striking single feature distinguishing the syphilitic group from the nonsyphilitic is that the death rate is higher among the syphilitic men. Exactly how and why more of the syphilitic group has died is not clearly discernible, but the penalty which the syphilitic patients have paid in terms of life expectancy is well documented.[5]

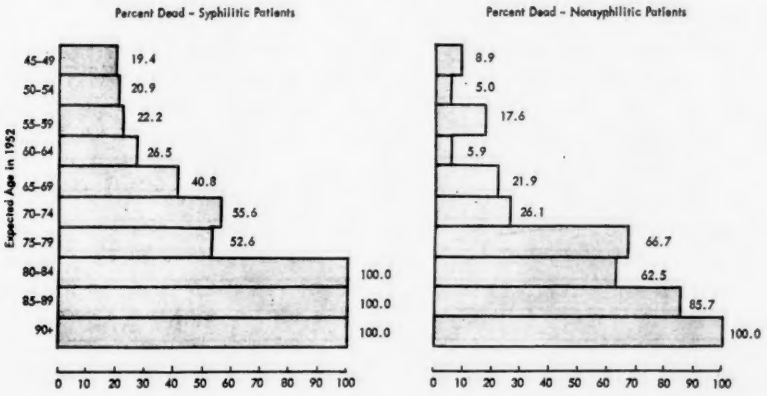

Fig. 3.—Mortality of syphilitic and nonsyphilitic patients, compared by percentage of each age group who have died during study period.

In Fig. 3, the mortality percentages of the deceased, by age group, are compared. Here again is seen the higher mortality of the syphilitic patients in each age group, with the exception of the 75- to 79-year-old category, where the death rate for nonsyphilitic is higher than that for syphilitic men. Such a difference serves to point out how the diseases of the aged enter the picture and seem to level the differences in the mortality experience of the men as they enter their later decades.

THERAPY RECEIVED BY SYPHILITIC PATIENTS INTERVIEWED IN 1952

It was expected that medical histories of the men in the study would reveal that they had received large amounts of antibiotic therapy for nonsyphilitic as well as syphilitic conditions. Questions were asked specifically as to time, source, duration, and amount of antibiotics received. Most of the men steadfastly denied receiving any antibiotic. As the same interviewing techniques were applied to nonsyphilitic as well as to syphilitic subjects, it was reassuring to discover that the antibiotic treatment rates of the two groups, according to historical data, were comparable: 27.5 per cent of the syphilitic patients examined in 1952 had received penicillin in varying amounts as compared to 32.6 per cent of the nonsyphilitic patients examined. The explanations for this low rate of exposure to antibiotics in this antibiotic era of medicine apparently are:

1. The economic plight of these men, who generally lack the means to afford medical care.

2. The relative well-being and hardiness of this aging but sturdy group of farmers.

3. The stoicism of these men as a group; they still regard hospitals and medicines with suspicion and prefer an occasional dose of time-honored herbs or tonics to modern drugs.

Many of the men have never been examined by any physician other than the Public Health Service officer who comes to Tuskegee periodically for surveys. Even these physicians had to overcome the apathy of the men at first, until they became accustomed to the examinations.

It is the practice of Public Health Service officers to refer men who develop syphilitic or nonsyphilitic conditions requiring therapy to the proper sources of treatment. Nevertheless, a few of the men have, on their own, sought and received antisyphilitic treatment in varying amounts. Some were treated by private physicians, a few had been inadvertently rounded up and sent to rapid treatment centers by health department workers who were unaware of the research project. Some of the patients were given therapy because of positive serologic tests for syphilis (STS) or because of a history of infection; some even were treated for unrelated symptoms, rather than for specific complications of syphilis.

In Table III, a comparison is made of 8 subjects who received antisyphilitic treatment: of disease duration in relation to treatment, serologic tests, and age. These 8 men were selected from the total of 12 syphilitic patients who have a history of adequate treatment. Their histories exemplify some of the problems encountered in this study. Patient 225 was the first man in our group to receive penicillin, which was given to him for a nonsyphilitic condition (pneumonia); after fourteen years of inadequately treated syphilis, his STS became negative following adequate treatment. Patient 097, 71 years of age, was seroresistant after adequate treatment, which is not difficult to explain since he had already lived with his untreated syphilis for forty-seven years and had submitted to therapy only because it was advised "as a premarital precaution."

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The arsenical treatment listed is small, and, according to quantitative standards agreed upon for the Sing Sing study,[13] less than 12 injection units can be regarded as "no treatment" (an injection unit is one injection of arsenical or two of bismuth). When the years of untreated syphilis are calculated for each man by subtracting the date of lesion from the date of treatment, and the total of the differences considered, we find 123 years of untreated syphilis and 107 years of inadequately treated syphilis compared to 20 years of adequately treated disease. Note that these sums are obtained from analysis of histories of 8 of the men who had been treated, and who, at first glance, would have been dropped from a study of untreated syphilis.

TABLE III. MEDICAL HISTORY OF LESIONS AND THERAPY OF EIGHT SYPHILITIC PATIENTS WHO WERE EXAMINED IN 1952; SHOWING DURATION OF DISEASE BEFORE TREATMENT WAS RECEIVED

PATIENT CHART NUMBER	HISTORY OF LESION (DATE)	ARSENICAL		DATE OF ADEQUATE PENICILLIN TREATMENT	DISEASE DURATION IN YEARS			KAHN REACTION		AGE IN 1952
		NUMBER	DATE		UNTREATED	INADEQUATE TREATMENT	ADEQUATE TREATMENT	PRIOR TO TREATMENT	AFTER TREATMENT	
137	1924	5	1934	1951	10	17	1	negative	negative	45
188	1928	7	1934	1949	6	15	3	doubtful	doubtful	45
225	1933	8	1934	1947*	1	13	5	positive	negative	55
534	1922	8	1934	1949	12	15	3	doubtful	doubtful	52
540	1928	5	1934	1949	6	15	3	doubtful	negative	53
034	1915	6	1935	1951	20	16	1	positive	positive	62
239	1913	8	1934	1950	21	16	2	doubtful	negative	68
097	1903	0	—	1950†	47	0	2	positive	positive	71
Total years					123	107	20	3 of 8 became seronegative		
Average years					15.4	13.4	2.5			

*Penicillin received for 2 weeks continuously, for pneumonia.
†Therapy given to 71-year-old man as a premarital precaution.

In Fig. 4, the treatment status of 160 syphilitic men, who furnished reliable treatment histories, is analyzed according to the amount and adequacy of therapy, on the basis of the categories recommended by the workers in the Sing Sing study.* The surviving syphilitic group is now 70 per cent untreated, 22.5 per cent inadequately treated, and 7.5 per cent adequately treated; this is compared to 100 per cent untreated in 1932 when the study was begun.

In Table IV, therapy status in 1952 is designated by age groups.

*The Sing Sing criteria for "no treatment" is no treatment, or treatment of less than three months' duration with arsenicals and bismuth, or less than 12 injection units of arsenicals and/or bismuth. "Inadequate treatment" is treatment for three to ten months, or 12 injection units or more, but less than "adequate" treatment, or less than 2,400,000 units of penicillin. "Adequate treatment" is 20 injections each of arsenicals and bismuth, or 30 injection units within two years, or any completed rapid treatment schedule consisting of 2,400,000 units or more of penicillin.[13]

TABLE IV. THERAPY STATUS IN 1952 OF 160 SYPHILITIC PATIENTS WHO WERE EXAMINED

AGE IN 1952	NUMBER OF PATIENTS	UNTREATED	ARSENICALS		PENICILLIN	
			3 TO 11	12 TO 22	INTER-MITTENT	CONTIN-UOUS
45 to 49	39	4	22	1	9	3
50 to 54	19	3	9	1	2	4
55 to 59	22	7	11	1	2	1
60 to 64	20	7	6	0	5	2
65 to 69	27	13	5	1	7	1
70 to 74	15	10	1	0	3	1
75 and over	18	13	1	0	4	0
Total	160	57	55	4	32	12
Per cent	100.0	35.6	34.4	2.5	20.0	7.5

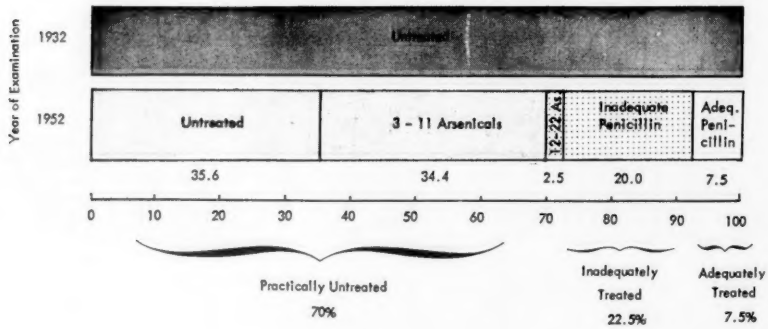

Fig. 4.—Specific therapy (classified according to Sing Sing study criteria, as described in text) received by syphilitic patients who were examined in 1952, as compared to untreated status of patients in 1932.

Fig. 5 compares age groups among the syphilitic men in terms of average man-years of untreated disease for each group. As, in Table V, the date of lesion is subtracted from date of therapy to obtain the number of years of untreated disease, so the number of such years for a given age group is divided by the number of individuals in that group to give an average. The average man-years of untreated disease are then plotted as a bar graph. The average syphilitic patient in the youngest age group (45 to 49 years of age) has had untreated disease for only 25.4 years, compared to the average man in the oldest age group (75 years of age and older) who has survived 49.6 years of untreated syphilis. Thus, modern treatment has altered this untreated syphilis study and made the task of analysis more complex. The task, as we see it, is not to discard all patients who have received any treatment, but rather to record as specifically as possible each date of injection and amount of therapy received. It does not seem warranted to underestimate the importance of following these syphilis

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survivors indefinitely, since even in 1952 they are veterans of an aggregate of 5,494.5 man-years of untreated disease, in comparison to only 28.5 man-years of adequately treated disease.

TABLE V. DURATION OF SYPHILITIC DISEASE BY AGE GROUPS IN 1952; 160 PATIENTS

AGE IN 1952	NUMBER OF PATIENTS	MAN-YEARS OF DISEASE			AVERAGE MAN-YEARS BY TREATMENT STATUS		
		UNTREATED	INADEQUATE TREATMENT	ADEQUATE TREATMENT	UNTREATED	INADEQUATE TREATMENT	ADEQUATE TREATMENT
45 to 49	39	989	19.5	4.5	25.4	0.5	0.1
50 to 54	19	487	21	12	25.6	1.1	0.6
55 to 59	22	711	18	5	32.3	0.8	0.2
60 to 64	20	706	9	2	35.3	0.4	0.1
65 to 69	27	1,062.5	30.5	3	39.4	1.1	0.1
70 to 74	15	646	6	2	43.1	0.4	0.1
75 and over	18	893	18	0	49.6	1.0	—

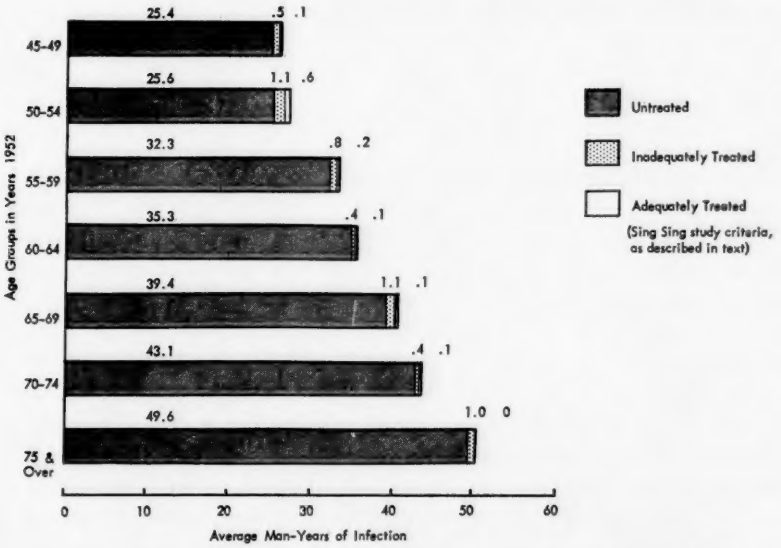

Fig. 5.—Average man-years of syphilitic infection among those examined in 1952, by treatment status and age groups.

Since the man-years of adequately treated disease represent such a small part of the total years of observation, and in most patients the treatment was administered many years after the date of the original infection, it is felt that the antibiotic era has not defeated the purpose of the study. Essentially, the study continues to be concerned with the effects of untreated syphilis, and on this basis, in certain of the papers in this series, the original syphilitic group is treated as an entity, regardless of the kind or amount of treatment.

MEDICAL HISTORY

Each patient was interviewed by both the physician and the interviewer-investigator. The chief complaint in each case was recorded. Most of the younger men had no complaints other than an occasional half-humorous reference to decreasing libido. Among the older men, complaints of backache and rheumatism were most frequent, even in several patients where clinical evidence of heart enlargement would suggest that cardiac symptoms could be expected. An attempt was made to estimate whether the individual seemed to be stoically inclined or hypochondriacal. As a whole, these men may be characterized as being almost as resigned to the infirmities of the flesh as they are to the vagaries of weather conditions which influence their crops; and they complain somewhat more vociferously about the latter. As in the past, the physician asked pertinent questions to elicit any cardiac symptoms, such as dyspnea, orthopnea, and angina. In an attempt to obtain as much specific information as possible, the interviewer would persist in questioning until he received answers such as this one from a 69-year-old farmer: "Well, with my old mule, I can plow all morning without resting, but with my young mule, it's a lot different." In this farmer's case, the pertinent fact is that he was plowing day after day with *any* mule! Crude as such interviewing techniques may seem, we were striving to evaluate cardiovascular syphilis in these men in terms of disability and distress, as well as in terms of mortality.

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PHYSICAL EXAMINATIONS

All of the Alabama men were brought to the modern Veterans Administration Hospital in Tuskegee and were examined by a Public Health Service physician. Whenever diagnostic questions arose, consultation with specialists in ophthalmology, neurology, and cardiology was readily available and often utilized. As in past surveys, it was felt that a single clinical observer had the advantage of seeing the patient as a whole; this advantage might be lost if the patients were seen by a series of specialists who would be unknown to, and possibly mistrusted by, the patients. Examinations were limited to three or four a day to facilitate thoroughness.

Physical examination included the review of systems, blood pressure determinations from both arms, funduscopic examinations, and neurologic examination. As in previous surveys, the heart was examined with great care. For the first time in the study, stethographic records were obtained on each patient, the heart sounds were amplified and recorded synchronously with electrocardiograms and carotid artery pulse curves.* With stethographic records, the timing of suspicious murmurs was facilitated, and the recordings were a constant stimulus to the clinician to perform his best work so that the machine might not discover a murmur which he had missed. One factor of importance was the positioning of the patient. The best stethographic records could be obtained from the aged men only when they lay supine and relaxed on the couch. Nevertheless,

*We wish to acknowledge the skill and advice furnished at the beginning of the survey by Dr. Henry Eisenberg (Surgeon, U. S. Public Health Service) who instructed our technician, Mr. William C. Bowie, of the Veterans Administration Hospital, in obtaining the best possible stethographic records.

it is probable that a few aortic murmurs might have been accentuated by having the patient sit up, lean forward, and exhale forcibly, as was done for auscultation. Having the patient exercise was useful, also, in auscultation, but impractical for our stethographic purpose.

Blood was drawn from syphilitic and nonsyphilitic individuals alike for VDRL slide and Kahn quantitative testing, as well as for the *Treponema pallidum* immobilization (TPI) test. All serologic tests for syphilis were performed at the Venereal Disease Research Laboratory at Chamblee, Georgia.

Spinal fluid examinations were done in 1951-1952 on only a few patients in whom it was felt to be definitely indicated by clinical findings. Omission of the test from the routine examination was made with great reluctance, since lumbar punctures had been done in 1932 on 271 of the original 408 syphilitic patients examined.[1] After twenty years, comparison of spinal fluid results with newer serologic techniques in the survivors would have been interesting. However, the emphasis in this survey upon epidemiologic tracing of every man made it impractical to employ a test which had been frightening to some superstitious patients, and, which might actually have driven them into hiding.[9]

DISCUSSION

It seems appropriate, after twenty years of experience, to comment upon some of the operational aspects of this study, which, to our knowledge, is the first prospective longitudinal long-term study involving the ideal of 100 per cent observation of a large group of diseased and control patients through life to autopsy.

Following these individuals through to autopsy is unique in a field study of this type, an autopsy rate of about 60 per cent of those who died is comparable to rates found in many teaching institutions. This phase of the study was made possible only because of the willingness of a private philanthropy, the Milbank Memorial Fund, to give moral commitment to such a lifetime study in order to make funds available for burial expenses and autopsy expenses. Without this suasion it would, we believe, have been impossible to secure the cooperation of the group and their families. Such private funds, committed for years in advance (and by an institution whose policies do not change with administrations or with single individuals, but which reflect decisions of technically competent boards of directors), would seem to be increasingly important for providing the type of support needed for the successful conclusion of similar studies in chronic disease.

A further factor to be considered is that of scientific interest on the part of the individuals concerned with working with the study. The one who sets up such a study may well assume that he, himself, may be dead by the time that the lifetime of many of the group is finished. The results of observation which will add to the sum of scientific knowledge may not begin to become available until years later; and at a time when the originator may be working in other fields and completely separated from the study. Those who contribute in the associated fields, in this case pathologic and serologic, add data which will be used years later by new investigators coming to the study; so that the early years,

and indeed the larger part of such a program, yield little in the way of scientific credit for those having the vision, perspective, and ability to plan and work so well. Under these circumstances it is probably necessary for such ventures to be undertaken cooperatively, as was this one, with the early workers being given an opportunity to engage in other activities having prospect of earlier fruition.

Continuing close association of persons locally trusted and liked by the study group is essential to the success of a project.

A quality of dedication to the ideal of a long-term study based upon love of and respect for the dignity of the individual within the group, and upon the satisfaction of making a single, valuable contribution to the increment of knowledge, without concern for credit, is fundamental and must exist in the research team. In this case, such qualities are found particularly in the local group who have been associated from the start. Without such personnel, intimately associated with the patients, without proper rapport between outside specialists and the patient community, and without mutual trust, understanding, and respect between local workers, outside specialists, and the central office, success cannot be assured, nor will continuity of observation be achieved.

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Finally, it is essential to consider changes in medical practice and knowledge over the long period of such a study. A prospective study is of value only if the original diagnoses are sound—if the original medical work is well based. In this instance, diagnoses were based upon the best medical practice and knowledge available at the time. Review, 20 years later, of history, physical findings, and laboratory work of the original records reveals evidence of the high quality of medical skill which was exercised. When this is coupled with performance of newer laboratory procedures, there is added evidence of the firmness of original diagnosis. The syphilitic group, re-examined, is now confirmed to be predominantly syphilitic, and the control group to be free from evidence of syphilis.

The primary purpose of this study was, and continues to be, the determination of the outcome of untreated syphilis. However, in the accomplishment of this purpose, certain factors have been brought to light which merit discussion in relation to long-term disease studies in general.

One of the most important of these factors, and also one of the most difficult to control, is the consistency of techniques and standards used in the evaluation process. As an example, the STS, originally used for diagnostic purposes, was found during the course of the study to be of particular interest in relation to the occurrence of spontaneous cure and in the establishment of serologic trends for comparison with such factors in treated syphilis. Unfortunately, only a partial picture of the serologic pattern in this study group could be determined, due to the lack of consistency in the type of serologic test used and in the level of antigen sensitivity. Newer and more improved versions of the same test procedure may be added during the course of a study, but continuity of the original measurements by the original technique must be maintained along with these additions if meaningful results are to be obtained.

Another factor of particular importance is the preservation of all records and materials. For instance, the retention of pathologic specimens after the

original interpretation has been recorded makes it possible to review stained slides and to prepare new ones in accordance with improved techniques and methods of interpretation. Arrangements at the outset of a study for the preservation of all pathologic material will permit the review of an entire patient series at one time, applying identical techniques and criteria.

SUMMARY

1. This report, one of a series relating to the effect of untreated acquired syphilis in the male Negro, contains a history of the study and a description of the current status of the study population.

2. Included in the present study group are 408 syphilitic individuals and 192 nonsyphilitic controls who have maintained their status since the beginning of the study. Of the 408 in the syphilitic group, 51 per cent are living, 39 per cent are dead, and 10 per cent are of unknown status. In the nonsyphilitic group, 65 per cent are living, 26 per cent are dead, and 9 per cent are of unknown status.

3. On the basis of the individuals examined during the 1951-1952 survey, it is estimated that 70 per cent of the syphilitic group have remained untreated, 22.5 per cent have had inadequate treatment, and 7.5 per cent have been adequately treated. However, in terms of man-years, the study represents an aggregate of 5,494.5 man-years of untreated disease, 122 man-years of inadequately treated disease, and 28.5 man-years of adequately treated disease.

4. Physical examinations in this survey consisted of a review of the body systems, blood pressure determinations, funduscopic examinations, and neurologic examinations. Stethographic and electrocardiographic records were obtained on the patients.

5. Blood was drawn from syphilitic and nonsyphilitic patients for VDRL and Kahn quantitative testing, as well as for the TPI test.

6. This report has been prepared for the purpose of presenting information relating to the study group, which will serve as a basis for the discussion of the results of twenty years of clinical observation, to be presented in a subsequent report.[7]

REFERENCES

1. Vonderlehr, R. A., Clark, T., Wenger, O. C., and Heller, J. R., Jr.: Untreated Syphilis in the Male Negro. A Comparative Study of Treated and Untreated Cases, J. Ven. Dis. Inform. **17**:260, 1936.
2. Heller, J. R., Jr., and Bruyere, P. T.: Untreated Syphilis in the Male Negro. II. Mortality During 12 Years of Observation, J. Ven. Dis. Inform. **27**:34, 1946.
3. Diebert, A. V., and Bruyere, M. C.: Untreated Syphilis in the Male Negro. III. Evidence of Cardiovascular Abnormalities and Other Forms of Morbidity, J. Ven. Dis. Inform. **27**:301, 1946.
4. Pesare, P. J., Bauer, T. J., and Gleeson, G. A.: Untreated Syphilis in the Male Negro. Observation of Abnormalities Over 16 Years, Am. J. Syph., Gonor. & Ven. Dis. **34**:201, 1950.
5. Shafer, J. K., Usilton, Lida J., and Gleeson, G. A.: Untreated Syphilis in the Male Negro. A Prospective Study of the Effect on Life Expectancy, Milbank Mem. Fund Quart. **32**:262, 1954, and Pub. Health Rep. **69**:684, 1954.
6. Olansky, S., Simpson, L., and Schuman, S. H.: Untreated Syphilis in the Male Negro. Environmental Factors in the Tuskegee Study, Pub. Health Rep. **69**:691, 1954.

7. Olansky, S., Schuman, S. H., Peters, J. J., and Smith, C. A.: Untreated Syphilis in the Male Negro. Twenty Years of Clinical Observation of Untreated Syphilitic and Presumably Nonsyphilitic Groups. (To be published.)
8. Peters, J. J., Peers, J. H., Olansky, S., Cutler, J. C., Gleeson, G. A.: Untreated Syphilis in the Male Negro. Pathologic Findings in Syphilitic and Nonsyphilitic Patients, J. CHRON. DIS. **1**:127, 1955.
9. Rivers, E., Schuman, S. H., Simpson, L., and Olansky, S.: Twenty Years of Follow-up Experience in a Long-Range Medical Study, Pub. Health Rep. **68**:391, 1953.
10. Bruusgaard, E.: Über das Schicksal der nicht spezifisch behandleten Luetiker, Arch. f. Dermat. u. Syph. **157**:309, 1929.
11. Gjestland, T.: The Oslo Study of Untreated Syphilis, Acta dermat.—venereol. (Supp. in press.)
12. Rosahn, P. D.: Autopsy Studies in Syphilis, J. Ven. Dis. Inform. (Supp. 21), pp. 1-67, 1947.
13. Kaplan, B. I., Cutler, J. C., and Gleeson, G. A.: Results of Therapy of Syphilis in a Prison Population. I. Long-Term Clinical and Serologic Studies on Outcome of Therapy for Latent and Asymptomatic Syphilis. (To be published.)

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Reviews

THE USE OF HORMONES IN RHEUMATIC DISEASES

R. H. FREYBERG, M.D.

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CORTISONE and corticotropin have been available for general use by the medical profession for approximately five years. During this period a vast amount of investigation of these and related substances has been conducted, and the clinical experiences have been sufficient in number and duration to allow a fair and meaningful assessment of their therapeutic value and limitations in the field of rheumatic diseases. Such is the purpose of this article. Specific data from individual investigations, statistical analyses, highly controversial considerations, and, especially, personal prejudices of individual investigators will be avoided whenever possible. Obviously, all the literature pertaining to this field of medicine cannot be condensed into a review of this size. It is hoped that important considerations and well-documented reports can be pointed up in a way that may be helpful for the medical practitioner.

The clinical problems relating to the administration of these hormones can be more readily appreciated if the fundamentals of their nature and pharmacology are thoroughly understood. A brief discussion of these fundamentals, therefore, is appropriate.

THE NATURE OF CORTISONE AND HYDROCORTISONE

Steroid is a generic name for certain tetracyclic compounds, some of which occur naturally; others are synthesized. The sterols are tetracyclic compounds which are monohydroxy alcohols of steroids; of this group, cholesterol is the best known.

Cortisone (17-hydroxy, 11-dehydrocorticosterone) is one of many steroids produced in the cortex of the adrenal gland. As the adrenal steroids were isolated, they were designated Compounds A, B—, and so on. Several of these adrenocortical steroids have been synthesized from precursors obtained from animal or plant source. At first, the synthesis employed desoxycholic acid obtained from ox bile as the starting substance. Later, methods for synthesis were developed from other sources including the Mexican yam, saponins, and digitalis derivatives.

The nucleus for all the adrenocortical steroids is shown in Fig. 1. Changes in the steroid structure can be made in the ring system and in side chains.

Formulas for some of the more important steroids are shown in Fig. 2. Note their striking similarity and that they differ only in small changes, sometimes only by the addition or subtraction of a single atom. For instance, the structure of cortisone is the same as that of hydrocortisone except for an H atom at position carbon eleven. Such small differences, however, may greatly alter the chemical, physical, and physiologic properties of the steroid.

These compounds are divided into two main groups according to the presence or absence of an O atom at the C_{11} position; those which contain oxygen are designated the "oxycorticosteroids," those which do not are "desoxycorticosteroids." Certain general physiologic properties are common to each of these classes of steroids.

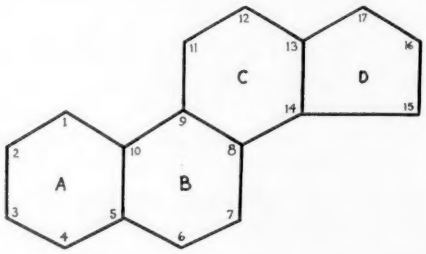

Fig. 1.—The steroid nucleus.

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THE NATURE OF CORTICOTROPIN

The production and secretion of the adrenocortical steroids can be increased profoundly by stimulation of the adrenal cortices by the adrenocorticotropic hormone (ACTH) of the pituitary gland. This pituitary hormone, now designated "corticotropin," is known to be a complex protein (polypeptide) structure whose exact chemical formula is not known, and it has not been synthesized. Where corticotropin is injected into an animal with intact adrenal glands, the physiologic effects are similar to those produced by the direct administration of the active adrenocortical steroids.

PREPARATIONS FOR THERAPEUTIC USE

Prepared by partial synthesis, cortisone and hydrocortisone are creamy white crystals or crystalline powder, relatively insoluble in water and physiologic solutions. For injection purposes, microcrystals of the steroid, or a salt of it, are suspended in an aqueous medium or dissolved in dilute alcholol solution. The crystals are also compressed into tablets for oral administration. All these preparations are stable at room temperature.

Cortisone.—All commercial preparations of cortisone contain this steroid in the acetate form. Aqueous suspension of cortisone, 1 ml. containing 25 mg., is used for intramuscular injection. With the later demonstration[1] that this

steroid was effective when administered orally, it has commonly been used in tablet form. Scored tablets containing 5, 10, and 25 mg. of cortisone acetate are available so that doses varying by as little as 2.5 mg. can be prescribed.

Hydrocortisone.—Clinical trials have indicated that hydrocortisone is effective when given orally or parenterally. Injected intramuscularly or intravenously, or given orally, this steroid in the plain alcohol form (not the acetate salt) has been most effective. A suspension containing 25 mg. per milliliter is available, but is seldom used intramuscularly. A special concentrated solution containing 100 mg. of the steroid in 20 ml. of alcohol has been available recently, for intravenous use. It is to be diluted in at least 500 ml. of sterile water, normal saline, or glucose solution and given slowly by infusion. This preparation is ideal for administration to nauseated or unconscious patients who urgently need it.

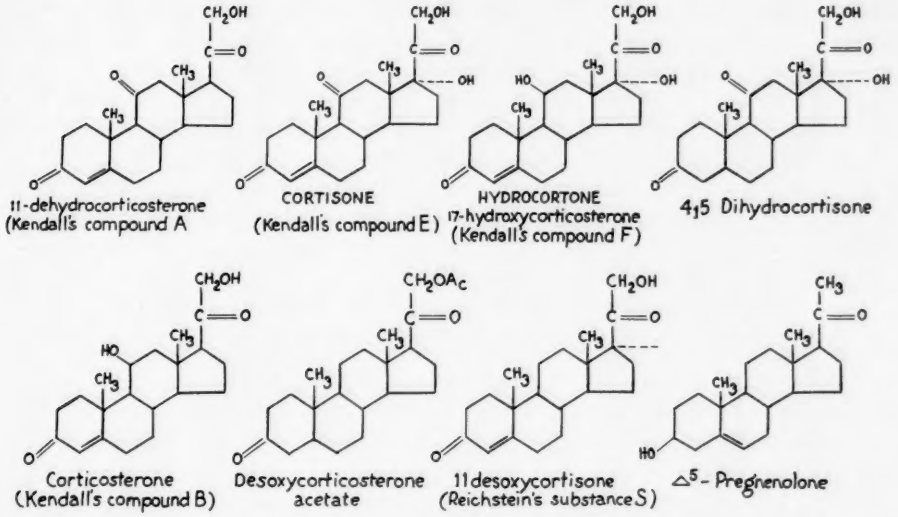

Fig. 2.—The structural formulas for cortisone, hydrocortisone, and several closely related steroids.

Tablets of hydrocortisone containing 5, 10, and 20 mg. are generally available, and are often used in perference to cortisone acetate because there is evidence[2] that this steroid may be more potent. Initially, it was thought that it may be twice as potent, but as more experience has been gained, it appears that in most patients the ratio of therapeutic effectiveness is about 80 per cent, so that a tablet containing 20 mg. of hydrocortisone is usually equivalent to 25 mg. of cortisone acetate. Although in most patients there is little or no difference between equivalent doses of these steroids, occasionally it is found, for unknown reasons, that one is either tolerated better, or is decidedly more effective.

Local Use of Hydrocortisone.—Hollander[3,4] and others[5,6] have shown that hydrocortisone acetate has a dependable anti-inflammatory effect when injected into the cavities of joints, bursae, and tendon sheaths. A suspension containing

25 mg. in 1 ml. is well tolerated and convenient to use. The acetate of hydrocortisone is more dependable than the cortisone salt for this manner of use. When injected into a joint cavity its effects are (for practical considerations) only local, which gives it the advantage of being acceptable in a patient who cannot or should not have the steroid used systemically. By the same token, its benefits are sharply restricted to the site of injection, which limits its practical usefulness to only one or two joints at one time. Sterile precautions should be exercised in order to prevent the introduction of infection into the joint during the injection.

Corticotropin.—For some time the only preparation of corticotropin (ACTH) available for clinical use was a dry powder which had to be mixed with sterile water or saline solution for intramuscular use. The effects of this solution were of short duration, usually disappearing in six hours, and for more prolonged effects, it was necessary to inject a dose three or four times daily. Later, corticotropin has been incorporated into a gel; when this is injected intramuscularly the absorption is delayed and the effects continue for twelve hours or longer. More recently, it has been shown that an intravenous infusion of corticotropin given slowly over a period of six hours is still more efficient. So given, 25 mg. of corticotropin daily will produce effects equivalent to those of 100 mg. daily divided into four intramuscular injections. The practical use of such a slow intravenous infusion is limited. Corticotropin is ineffective if administered orally.

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THE PHYSIOLOGIC AND PHARMACOLOGIC ACTIONS OF CORTISONE AND HYDROCORTISONE

The action of cortisone and hydrocortisone is complex and not fully understood. The physiologic effects of these steroids are essentially the same. Because these effects were first identified with cortisone, it is common practice to speak of the "cortisone effects," meaning the effects of either cortisone or hydrocortisone. To spare repetitious mention of both steroids, this practice will be employed in the following discussion.

Metabolic Effects.—An increased amount of cortisone in the body, whether administered directly or as a result of stimulation of the adrenal glands by injection of the anterior pituitary hormone, corticotropin, causes alterations in numerous metabolic processes, involving both electrolytes and organic metabolites. Generally, there is retention of sodium and water, which may be sufficient to result in edema. There is increased elimination of potassium in the urine, and this may decrease the tissue potassium. Chloride may be retained with sodium, or excreted with potassium. Excretion of calcium and phosphorus is increased and if this continues for a prolonged period osteoporosis may result. The catabolism of protein is increased so that a negative nitrogen balance and wasting of muscle tissue result. The excretion of uric acid and creatinine is increased. Glyconeogenesis is enhanced and there is increased deposition of glycogen in the liver. The effect of insulin is inhibited, carbohydrate combustion is impaired, and in some instances the blood sugar is increased and

glycosuria occurs. Adipose deposition may be increased and the level of ketone bodies in the blood may be elevated.

Endocrine Effects.—Cortisone produces various interhormonal changes. Characteristics of Cushing's syndrome appear after prolonged cortisone administration: rounding of the face (moon face), large jowls, dorsal fat pad, obese abdomen, striae in the stretched skin, acne, and hirsutism. When cortisone is administered, the physiologic "need" stimulus for its production does not exist, and as a result the pituitary secretion of corticotropin decreases and the adrenal cortical function becomes suppressed. The function of the thyroid may be depressed. Menstruation may be suppressed or completely inhibited with resulting menopausal symptoms.[7]

Effects on the Blood and Circulation.—The bone marrow is stimulated to produce an increased number of erythrocytes and neutrophils. The production of lymphocytes is decreased and lymph tissues may decrease in size. There is a decrease in the number of circulating eosinophils; however, this effect is variable in degree and occurs at different speeds.

Blood pressure frequently is elevated, sometimes to hypertensive levels. Prothrombin time may be decreased, enhancing thrombosis.

Enzymatic Changes.—Cortisone has the ability to increase the production of pepsin and trypsin and to decrease the production of lysozyme. Hyaluronidase activity is decreased by cortisone.

Effect on the Central Nervous System.—Changes in function of the nervous system are indefinite and unpredictable. Euphoria is very common. Nervous tension, an uncomfortable sense of being driven, and insomnia frequently occur with large doses of cortisone. Changes of mood may occur and psychomotor activity may become altered. Excitation or depression may appear, sometimes in the proportion of major psychoses.

Antiallergic and Anti-inflammatory Actions.—The effects of cortisone which account for most of the clinical benefits are the antiallergic and anti-inflammatory actions. Different ways have been suggested to explain how cortisone can alter antigen-antibody reactions so as to benefit an allergic state. The studies of Wedgewood, Hawn, and Janeway[8] indicate that the antiallergic action of corticotropin takes place directly in the cells of the end organ ("shock organ"). Rich[9] has found essentially the same effect with cortisone.

In tissues, cortisone suppresses the inflammatory response to practically all forms of irritation. It decreases the magnitude of the entire inflammatory process: vasodilation, hyperemia, capillary permeability, cellular exudation, leukocyte infiltration, phagocytosis, and fibroblastic proliferation. The cardinal signs of inflammation—swelling, redness, heat, and pain—are alleviated. Rose and his associates[10] suggested that the basis for these effects may lie in the increased destruction or decreased local production of histamine. These reactions inhibit first the formation of the usual lymphocytic barrier and, later, of the fibroblastic barrier to the injurious agent. Thus, the natural lines of defense are suppressed. The net effect of cortisone on injured or inflamed tissue is the

tendency to diminish the reaction to the injurious agent while doing little to prevent its invasion of surrounding tissue.

In very high and unphysiologic dosage, the inhibition of proliferation of mesenchymal tissue including fibroblasts may interfere with connective tissue repair and scar formation, as shown in animal experiments by Ragan and his collaborators.[11,12] In doses commonly employed clinically, the inhibition of fibroblast formation seldom is seen as an important action of cortisone.

Another cortical steroid which has physiologic effects comparable to those of cortisone is hydrocortisone. This steroid is now known to be secreted in the normally functioning or corticotropin-stimulated adrenal glands, in larger amounts than is cortisone, and is considered to be largely responsible for the effects earlier attributed to cortisone. One important difference in these two steroids is noted in the local use of the synthesized steroids.

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GENERAL CLINICAL CONSIDERATIONS OF CORTISONE

When the clinical effects of cortisone and corticotropin were first announced by Hench and his collaborators,[13] it was emphasized that they were reporting a physiologic experiment and they cautioned against an immediate attempt to use these substances for treatment. However, as supplies became plentiful and relatively inexpensive, it was natural that careful attempts be made to use these hormones for the benefit of patients with rheumatic disease. In the numerous reports discussing clinical trials, it is to be noted that the forms of rheumatism especially benefited by cortisone are those characterized by inflammation. The clinical benefits to the rheumatic state frequently are referred to as the "antirheumatic effects" and are due chiefly to the anti-inflammatory action of cortisone. This term should not be considered as meaning "analgesia" only, for although relief of pain is an important accompanying result, "antirheumatic" refers to the suppression of the inflammatory state of the rheumatic process and the improved physiology of the connective tissues.

The Antirheumatic Effects.—In all inflammatory types of rheumatism the antirheumatic effects of cortisone are similar and follow a definite pattern. There is great reduction of stiffness (nonarticular) which allows easier and greater range of motion, even in the inflamed joints. Pain at the joints and in the nonarticular connective tissue decreases or disappears. Swelling, tenderness, and heat at the inflamed joints progressively decrease. The time required for these changes to be effected varies from a few days in acute diseases to many weeks in the chronic and more severe forms of rheumatism. If treatment with sufficient amounts of cortisone is given early in the illness, all physical signs of inflammation disappear and normal function returns; in patients treated late in the disease, some swelling, effusion, or other evidence of inflammation usually persists although all symptoms frequently subside. Signs and symptoms of accompanying nonarticular disease (bursitis, tenosynovitis, nodules, and other nonarticular features) diminish or vanish concurrently with improvement in the joint synovitis. Destructive changes affecting cartilage or bone which commonly occur in long-standing chronic rheumatoid arthritis do not improve;

these are irreversible changes. Hence, thinning of articular cartilage, cystic changes in bone, osteoporosis, exostoses, calcification of ligaments, intra-articular ankylosis (fibrous or bony), and structural joint deformities remain unimproved. Indeed, new damages to cartilage and bone may develop during cortisone administration when suppression of the rheumatoid activity is incomplete. However, because of the many other improvements which occur, the joint deformities often are less disabling. Because the anatomic abnormalities at the joints are not changed, no improvement can be expected in the radiologic appearance of the joints.

While rheumatic abnormalities are improving, there is simultaneous improvement in the systemic manifestations of illness. If present, fever subsides; appetite improves and often becomes so large that there is an increased consumption of food with resultant gain in weight, strength, and general sense of well-being. A sense of euphoria is usually prominent and beneficial.

Laboratory abnormalities which characterize the disease change toward or entirely to normal. Anemia is partially or completely corrected, plasma proteins change toward normal; the globulin decreases and albumin increases. Almost invariably there is significant reduction in the rate of sedimentation of erythrocytes, and usually comparable to the amount of clinical improvement.

The three predominant attributes which characterize the cortisone effects are: (1) dependability of action; (2) speed of effect; and (3) the high order of benefit obtained. The degree of antirheumatic effect, like most other effects of the hormone, is directly related to the quantity of hormone administered. The action of the hormones can be finely regulated by adjustment of the dose so that the disease process can be decreased or allowed to increase quite at will. The antirheumatic effect continues as long as the administration of the steroid is continued, and in the rheumatic illnesses which are not acute and self-limited, relapse regularly occurs after use of the hormone is discontinued during an active disease. The speed and degree of relapse vary unpredictably.

Manner of Action.—The way in which cortisone produces this remarkable antirheumatic effect is not known. Although Dobriner[14] found certain foreign steroids and abnormal quantities of natural steroids in the urine excreted by rheumatoid arthritics, suggesting that some abnormality of adrenal cortical function may exist in these patients, there is no dependable evidence that any rheumatic disease is caused by dysfunction of the adrenal glands or by a deficiency of cortical hormones. The administration of cortisone to a rheumatic patient does not make up a deficiency of this steroid; instead, the administered steroid actually produces a state of hypercortisonism. *None of the known metabolic or hormonal actions of cortisone explain the manner of production of the antirheumatic effect.* The speed of improvement in the stiffness and pain, allowing remarkable increase in movement of joints that are still inflamed, strongly suggests that the benefit is obtained at the connective tissue level through the beneficial alteration of one or more enzyme systems. But what this is and how it is altered (if it is indeed the mechanism) are not known. Other possibilities considered include a change in antigen-antibody relationship or an alteration in tissue permeability. The basic pathologic process which causes the inflammation is not eliminated

by administration of cortisone, as is shown by the tendency for the activity of the disease to return after the administration of the steroid is discontinued. Thus, the effect of cortisone is seen to be suppression but not elimination of the disease state.

Complications.—The physiologic actions of the hormone may produce complicating problems (side reactions, toxic effects). These may be trivial and only minor nuisances, or of such serious magnitude as to preclude continued use of the hormone. The characteristics of Cushing's syndrome are only nuisance troubles. Potassium depletion may produce great troubles and edema of the lungs may be serious. Severe osteoporosis has been the basis for pathologic fractures. Disturbance of carbohydrate metabolism may be so great as to require discontinuance of use of the hormone. Accentuation of menopausal symptoms may be annoying. Peptic ulcer may develop with any of its serious complications. Nervous and mental complications have included nervous tension, insomnia, and (infrequently) major psychoses characterized by excitement, agitation, or depression. Complications are more frequent and may be more severe in female patients especially those in or near the menopause. This has become a matter of practical importance.

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During prolonged use of cortisone, adrenocortical function decreases significantly; this seldom produces any clinical problem during the continued administration of the steroid, but if administration of cortisone is stopped suddenly serious adrenal insufficiency may exist for many weeks, and this may be particularly troublesome during stressful situations.

Because cortisone inhibits the barriers to inflammation, intercurrent infections may be more invasive and a serious systemic infection may result. This complication is unusually hazardous because the cardinal signs of infection may be masked by the effects of cortisone, and there may be a disastrous delay in instituting appropriate treatment. Inactive tuberculosis may become activated.

All the undesired effects of cortisone are temporary in nature and produce problems only if use of the hormone is continued. The complications resolve after administration of the hormone is stopped. Animal experiments[15] have shown that atrophy of the adrenal glands disappears quickly after discontinuance of cortisone. The fear of permanent damage to the adrenal glands from prolonged use of cortisone, therefore, seems unjustified.

In the forms of rheumatism which are naturally of short duration, cortisone can be of great benefit to the patient and, because of the short period of use required, few difficulties result from undesired steroid actions. In a chronic disease, however, such as rheumatoid arthritis, greater problems accompany the use of cortisone; the underlying disease process is not eliminated, and prolonged, vigorous use of the steroid may produce important complications.

THE USE OF STEROIDS FOR SPECIFIC RHEUMATIC DISEASES

For the purposes of this discussion the rheumatic diseases may be divided into two groups: the acute, and the chronic forms of rheumatism. The use of hormones varies considerably depending upon the length of time treatment

is required. For prolonged use of any medication it is desirable that it be in a form that can be taken by mouth. But for acute illnesses, parenteral injection may be reasonably employed.

In this connection, it must be realized that cortisone effects can be obtained by stimulating the patient's own adrenal glands to increased secretion as well as by administering the steroids directly. Even though corticotropin (ACTH) requires injection, it can be a practical treatment procedure for the acute rheumatic diseases. Also, in the treatment of acute illnesses the likelihood of complications and undesired effects of cortisone is relatively small so that the doses may be larger than would be practical for chronic illnesses. These considerations will become apparent in the discussion which follows.

ACUTE RHEUMATIC DISEASES

Rheumatic Fever.—Numerous investigators report excellent antirheumatic effects from the use of corticone, hydrocortisone, or corticotropin in acute rheumatic fever.[16-23] Within 24 to 48 hours, signs of systemic illness lessen or completely disappear and there is a sense of well-being. The signs of joint inflammation quickly abate and the rheumatic symptoms disappear, so that movement of the joints is usually normal within a few days. All clinical signs of disease are usually gone within seven days; the erythrocyte sedimentation rate returns to normal more slowly, usually not before four to eight weeks, and the electrocardiogram improves still more slowly.

As is true for many diseases, the foremost question in relation to rheumatic fever is whether the steroid hormone is the best available form of treatment, with advantages not found after other forms of therapy. A study was undertaken to answer these questions, jointly by a committee of the British, Canadian, and American Heart Associations. A preliminary report[24] indicates that there were no significant differences in the effectiveness of salicylates, cortisone, or corticotropin therapy for comparable cases of rheumatic fever. However, it must be clearly recognized that the management of all patients followed a fixed protocol; no individualization of treatment could be made, and there are many points in which this preliminary evaluation may fall short of fulfilling a complete evaluation of each form of treatment.

The possible superiority of cortisone therapy lies in (1) a more rapid suppression of the disease process, (2) more effective control of the severe manifestations of the disease, especially carditis, and (3) prevention of organic cardiac sequelae. Whether any of these benefits are gained by the best therapeutic use of cortisone present knowledge will allow must await longer observation and more intensive study. There are many careful investigators who believe cortisone or corticotropin therapy is, in certain circumstances, superior to other forms of treatment. Holbrook[22] believes that corticotropin and cortisone are effective in reducing deaths from severe carditis, and that this is one circumstance when steroid therapy should be used. The long period (ten years in some cases) after active disease before cardiac sequelae may be recognized accounts for the uncertainty regarding this possible benefit of treatment with

steroids. It is, however, reasonable to think that the earlier the disease is suppressed the less likely significant scarring will result in the heart. Hence, the importance of the prevalent opinion that the earlier steroid therapy is started the better the results. There is good evidence to indicate that if treatment is begun late in the disease, or after the development of severe carditis, cardiac damage is usually not prevented or remedied. Wilson[22] has reported that the degree of residual cardiac damage is directly proportional to the duration of active carditis before treatment is instituted. The evidence suggests, therefore, that cortisone treatment is advantageous in active rheumatic fever the earlier it is instituted and when severe carditis exists.

The schedule of therapy cannot be standardized. It is best to use large doses early in the period of treatment. If corticotropin is employed, 80 to 100 mg. intramuscularly daily, in three or four divided doses, or 25 to 50 mg. daily in a slow intravenous drip over six to eight hours is appropriate. For children, the dose is not based upon body size, but rather on the severity of the disease, an evaluation not easy to make. After seven to ten days, the initial dose may be reduced by 25 per cent if signs of the disease are suppressed. If suppression continues, another reduction in dose of 25 to 50 per cent may be made fourteen to twenty days from the start of treatment. At comparable periods similar reductions can be made until treatment is discontinued after a total of three to eight weeks. Should relapse occur, treatment adequate to suppress the disease activity should be reinstituted.

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Cortisone acetate or hydrocortisone may be used initially or to replace corticotropin at any time. If cortisone is used from the start of treatment, a high dosage schedule has been advised,[23] 200 or even 300 mg. daily for from six to eight weeks. The steroid can be injected intramuscularly, but unless parenteral use is necessary because the patient is vomiting or irrational due to severe illness, injections have no advantage over tablets taken orally. By whatever route it is given, it is best to divide the daily medication into three nearly equal portions given at six- to eight-hour intervals. The injection of 40 to 50 mg. of corticotropin daily during the last few days of cortisone therapy and for a few days after it is stopped will ensure a quicker return to usual adrenocortical secretion and lessen the chance of postcortisone adrenal insufficiency.

In more ill and highly febrile patients, there is greater chance for potassium deficiency to develop. This can be prevented by the administration of 2 to 6 Gm. of potassium chloride daily, the exact amount to be determined by blood potassium determinations. In patients with carditis, circulatory embarrassment may exist so that greater care must be taken to restrict salt intake and to prevent sodium retention and edema.

Opinions vary regarding the length of treatment which is best for patients with acute rheumatic fever. A few patients do well with seven days of intensive treatment. For many patients, twenty-one days of treatment is adequate; for others fifty days of treatment may not be enough. Trial of stopping treatment after three or four weeks will indicate the course to follow. It seems quite clear that if steroid treatment is used for the period of active rheumatic fever, it should be instituted as early as possible, given in amounts sufficiently large

to suppress the disease and for a time long enough to allow the disease to become and remain suppressed.

After discontinuance of hormone therapy in patients with rheumatic fever, if the disease is still active, symptoms and clinical manifestations of inflammation will reappear within a few days, accompanied by an increase in the erythrocyte sedimentation rate and C-reactive protein in the blood. Should such a "rebound" occur, reinstitution of hormone therapy is advisable. Fischel and Frank[25] have reported that if salicylates are given simultaneously with hormones and continued after hormones are stopped when treating acute rheumatic fever, rebound can be prevented or its severity diminished.

As further studies in this field of medicine are made, the currently dubious points will undoubtedly be clarified.

Acute Bursitis.—Usually, acute inflammation of bursae is a rather minor and self-limited illness. In some cases, however, the inflammation may be difficult to control by conservative measures and, because of intense pain and local disability, use of cortisone or corticotropin may be warranted. When these drugs are used in large doses, the inflammation usually subsides within a few days, so that comfort is restored and normal function is regained. Corticotropin, 100 mg. daily intramuscularly for seven days, then reduced to 50 mg. or less daily, should suffice. Cortisone acetate, 200 mg. daily for one week, followed by 75 to 100 mg. daily until discontinued, is appropriate. Seldom is treatment required for longer than two or three weeks, during which time important undesired effects rarely occur.

If the inflamed bursa is so distended with fluid that a needle can be introduced into the bursal space, the injection of 25 mg. of hydrocortisone acetate suspension gives prompt and dramatic relief. A second or third injection after five to ten days may be appropriate. However, it has seldom been helpful to inject blindly small amounts of the steroid in the general vicinity of a painful bursa, hoping to get it close to the inflamed tissue.

If the bursal inflammation continues and becomes a chronic problem, or if tendonitis and/or periarthritis follow and greatly restrict motion (as not infrequently is the case especially at the shoulder), intense steroid therapy for two or three weeks may be beneficial in order to relieve the pain and stiffness, and to allow vigorous physical treatment to liberate the adherent tissue and restore the range of motion.

Acute Gouty Arthritis.—Corticotropin quite consistently suppresses a gouty attack quickly; cortisone, also, may produce quick relief. However, each of these hormones has failed in some cases. Usually a large dose of hormone—100 mg. of corticotropin or 300 mg. cortisone acetate daily given for a few days—is sufficient. Gouty synovitis may recur after discontinuance of the hormone unless colchicine is administered for some days after hormone treatment. Because colchicine or Butazolidin is usually extremely effective in quickly suppressing gouty inflammation and is so easily administered, it is now the concensus among investigators of this disease that corticotropin and cortisone should be selected for the treatment of gout for those patients who are intolerant

of or unresponsive to the chemotherapeutic agents named. A single injection of 25 or 50 mg. of hydrocortisone acetate into an acutely inflamed gouty joint may quickly arrest the inflammation and give complete relief.

CHRONIC RHEUMATIC DISORDERS

The use of steroids for *chronic* rheumatic diseases is accompanied by problems greater than those encountered in the treatment of acute disorders. Fundamental questions are: can cortisone or hydrocortisone be used safely and effectively to benefit patients with chronic rheumatic disorders? If so, what treatment schedule is best? The most important rheumatic disease for which these questions need be answered is rheumatoid arthritis.

Rheumatoid Arthritis.—At the beginning of clinical trials of hormone therapy for rheumatoid arthritis, three methods were considered worthy of trial:

1. Repeated administration of the hormone for relatively short periods separated by periods when no hormone was given.
2. Use of cortisone or corticotropin to suppress the disease and thereafter try to sustain the benefits by other means.
3. The use of cortisone or corticotropin for prolonged periods of time—many months or years—as "maintenance treatment."

The first plan was attempted with the hope that undesirable side effects would not occur, that adrenal and pituitary hypofunction would be avoided, and that with successive courses of treatment stepwise improvement in the arthritis might be obtained. However, although significant benefit regularly occurred during the time hormone was administered, relapse promptly ensued after the hormone was stopped, and after repeated courses of treatment there was no summation of benefit. This method was quickly abandoned.

The second plan failed since a suitable sustaining treatment could not be found.

The prolonged use of cortisone and hydrocortisone (Plan 3) has been extensively studied.[26-32] It is readily appreciated that the use of corticotropin, which requires intravenous injections daily or intramuscular injections once or more daily, is impractical for prolonged treatment unless the patient is hospitalized. Hence, most studies of prolonged treatment have employed cortisone or hydrocortisone orally.

The usual plan for prolonged or "maintenance" cortisone therapy has been about as follows: ample medicine is administered during the first seven to fourteen days to suppress the disease to a level which the patient and the doctor agree upon as satisfactory, after which a smaller dose is given daily to maintain this degree of benefit—the maintenance dose. It is to be emphasized that the desired effect is *not complete suppression* of the disease, which would require doses of cortisone too large for maintenance use. It is instead a partial suppression of rheumatoid activity, sufficient that the patient is comfortable and able to work, that is, a substantial rehabilitation. With this amount of improvement there are always some residual signs of rheumatoid activity, but less disability than before cortisone was administered.

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Following this plan of therapy, 150 to 225 mg. of cortisone acetate daily for three to seven days usually will accomplish a good partial suppression, after which 100 mg. daily for seven to fourteen days, then 75 mg. to 37.5 mg. daily, will maintain the effect in many cases. The steroid is more effective if the daily dose is divided into two or three portions. If the degree of suppression gradually lessens on the smaller dose schedule, the maintenance dose should be increased for a few days. The lowest dose that maintains the patient in comfort should be continued if tolerated well. The treatment must be individualized for each patient.

With such management, good to excellent antirheumatic effects are usually maintained *during* administration of the steroid. In only a small percentage of trials is long-term use of cortisone stopped because of poor therapeutic effect. In most instances a daily oral dose of 50 to 75 mg. of cortisone acetate is required for maintenance. If more than 75 mg. is required daily, it has been found[7] that important complications sooner or later make it impossible or undesirable to continue treatment. The variation in maintenance dose is correlated chiefly with the severity of the disease, not with its duration nor with the age, size, or sex of the patient. In amounts up to 75 mg. daily, maintenance cortisone acetate usually is well tolerated, with only minor undesired effects. Usually, complications can readily be corrected or controlled. However, the longer treatment is continued, the greater is the chance for serious trouble (peptic ulcer, gastrointestinal hemorrhage, hypertension, pathologic fractures, psychosis). It appears significant that the incidence and severity of complications are considerably greater among female patients. The chief benefit of hormone for the rheumatoid arthritic is *amelioration* of the disease.[27,32]

Although the benefits *during* treatment are usually gratifying, the difficulties *after* prolonged treatment sometimes are very disappointing to both the patient and physician. Within sixty days after stopping treatment, relapse to pretreatment level occurred in 84 per cent of my patients.[7] In many instances relapse starts even before the steroid is discontinued, after the daily dose has been reduced below 50 mg. It is noteworthy that patients with early disease relapse as promptly after discontinuance of cortisone as do patients with long-standing arthritis, indicating that early steroid therapy has no added virtue. Also, relapse occurs as often in those patients treated continuously for one year or longer as it does in those treated for a few months. This has led many investigators to plan to use cortisone indefinitely if it is considered wise to begin its use in a rheumatoid arthritic. As expected, adrenal function is suppressed in many patients after cortisone therapy is discontinued, but it returns to normal, as indicated by all available tests, within two to six weeks.

A very distressing postcortisone "withdrawal syndrome" occurs in some patients, especially if the steroid is abruptly discontinued. This complication, too, is more often encountered in female patients. The syndrome is characterized by severe and disproportionate stiffness and pain in joints and extra-articular connective tissue, weakness, fatigue, anorexia, hypotension, great discouragement, and depression. These patients are often miserable, bedridden,

and nearly helpless. The syndrome subsides in two to four weeks but some patients continue for many months to feel more ill than before treatment.

Whenever possible, it is advisable to discontinue cortisone gradually, since metabolic, endocrinologic, and psychologic adjustments are thus made more easily. A short period of corticotropin stimulation of adrenal function is usually helpful when cortisone is discontinued. Some patients who have no complication during treatment find it difficult to adjust psychologically and to the worsened rheumatic state after the "holiday" effected by cortisone.

Based upon such experiences, this type of prolonged cortisone treatment appears to be valuable for some, but not practical for all, patients with rheumatoid arthritis. Such treatment should not be planned routinely, but should instead be carefully selected for special purposes, such as a rapidly worsening disease not otherwise satisfactorily suppressed, and to facilitate physical treatment aimed toward rehabilitation of the disabled arthritic. The latter is a very important use of cortisone, only recently appreciated.

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Of the many problems that accompany the use of hormones for patients with rheumatoid arthritis, the most difficult is the question of when it should be used. It seems justified and wise to employ cortisone or hydrocortisone in the rheumatoid patients who are severely ill, whose disease is rapidly progressing and where other treatment has been inadequate, and when it appears that great discomfort and severe joint damages will incapacitate the patient. In other words, when the consequences of the disease appear to be more important than the potential troubles and risks of this potent treatment, hormone therapy is appropriate. Many patients have mild arthritis which is so well managed by conservative treatment that cortisone is unnecessary. In many large arthritis treatment centers, only 10 to 15 per cent of rheumatoid arthritics are treated with hormones. In some instances, the delicate decision "should cortisone be used or not?" can be made better by a specialist in rheumatic diseases. If hormone treatment is selected, it is advisable that the intelligent patient be informed regarding advantages and risks, the chances of benefit and failure, expense, and the nature and incidence of complications which may ensue.

Local Use of Hydrocortisone.—The intra-articular injection of hydrocortisone acetate is of practical value in the treatment of some patients with rheumatoid arthritis. The duration of effect is unpredictable: in some instances suppression of inflammation continues for many weeks after injection, in others, for only a few days. Similarly the degree of benefit varies considerably. Consequently, trial is the only way to learn whether this local use of hydrocortisone is of practical value. The likely candidates are: (1) those rheumatoid arthritics who have only one or two troublesome joints, (2) those in whom all but one or two joints have responded well to systemic treatment, (3) those in whom systemic treatment is contraindicated, (4) those patients who need orthopedic treatment to a deformed joint, or (5) the patients who need extensive physical treatment for rehabilitation.

The amount of steroid to be injected varies chiefly in relation to the size of the joint. In small joints of the fingers and toes 5 or 10 mg. gives excellent

results; in large joints (knee and hip) at least 25 mg., and often 50 mg., should be injected for best relief. Injection of more than 50 mg. at one time has proved impractical.

The benefits of intra-articular hydrocortisone continue for only a few weeks, so that repeated injections are needed for prolonged relief. Because the effect is only amelioration, an intelligent patient is the best judge as to the proper time for repeating the injection.

Variants of Rheumatoid Arthritis.—The considerations for the use of hormones in rheumatoid (ankylosing) spondylitis (Marie-Strümpell disease), psoriatic arthritis, and juvenile rheumatoid arthritis (Still's disease) are comparable to those encountered in the classical (peripheral) type of rheumatoid arthritis. In children with juvenile rheumatoid arthritis, the dose of cortisone is governed not by the size or age of the patient, but rather by the severity of the disease. Consequently, the dose required for a child usually approaches or equals that needed for adults. More complications occur in children than in adults receiving similar doses of cortisone or hydrocortisone.

Degenerative Disease of Joints.—It has been observed[33] that some patients with osteoarthritis of the hips experience relief of pain, increased motion in the arthritic joints, and an improved sense of well-being when treated with cortisone or hydrocortisone. It should be recalled that inflammation of connective tissue does not exist characteristically in this common form of joint disease, and when synovitis does occur it is very mild. Also, anatomic changes in the joints are irreparable. Hence, there is little or no opportunity for this rheumatic disease to be benefited by the anti-inflammatory effects of cortisone. The hormone can help such patients only by producing analgesia, by increasing muscle strength, and through a general tonic effect. For this noninflammatory type of joint disease, it should be appreciated that little benefit can be expected from systemic hormone treatment. Furthermore, in the majority of patients, degenerative changes at the joints produce slight discomfort and little disability so that it is unreasonable to select such potent medications for this relatively mild disease, especially when other forms of more conservative treatment are usually effective.

When it became obvious that hydrocortisone acetate suspension would exert a beneficial local effect when injected directly into a joint, it was natural to consider this method of treatment for the painful osteoarthritic joint, especially since so frequently only one or two joints are troublesome. Many trials have shown that generally the effect of intra-articular hydrocortisone is less beneficial in the osteoarthritic joint than in the joint affected by one of the types of inflammatory rheumatic disease. If there is significant synovitis secondary to the degenerative changes, as after trauma superimposed on osteoarthritis joint, or during the painful, developmental stage of the Heberden node, benefit may be significant, but such situations exist in only the minority of patients with osteoarthritis. The results are particularly disappointing in patients with *malum coxae senilis*, for whom it is often difficult to effect significant relief. Trials in a large group of these patients have shown that the

injection of steroid into the hip usually gives significant relief so seldom or for such a short time that either the patient or the doctor soon tires of this means of treatment. Still, for some patients this treatment is practical and effective, and trial in each candidate is the only means of evaluating it.

The technique, dose, and schedule of treatment are comparable to those discussed for other types of arthritis.

Miscellaneous Forms of Arthritis.—In the rarely encounted true *allergic arthritis*, corticotropin or cortisone may be helpful to suppress the attack because of their dependable antiallergic effects. The same is true for the *arthritis of serum sickness*. *Palindromic rheumatism* seldom causes sufficiently frequent or severe inflammation to require cortisone therapy. In a few instances, used as for rheumatoid arthritis, it has been effective in suppressing the disease. The intra-articular injection of 25 or 50 mg. of hydrocortisone acetate into the inflamed joint of the patient with *intermittent hydrops*, at the very beginning of the recurrent synovitis, has usually been very effective in aborting the attack. If such injections are made repeatedly at the beginning of each attack, in some patients the recurrences are less frequent and even cease, but this excellent response cannot be routinely expected. For "*psychogenic rheumatism*," hormone therapy is illogical.

Nonarticular Rheumatism.—A common form of chronic nonarticular rheumatism is the *fibrositis* syndrome. This is characteristically a minor illness, with relatively mild pain and stiffness which do not incapacitate the patient. Even though cortisone is frequently effective in relieving symptoms, usually it is unnecessary and unwise to employ this potent hormone for this nuisance disease.

If *periarthritis* of the shoulder follows initial bursitis, tendonitis, or "shoulder-hand syndrome," remarkable limitation of motion may result. In such instances of painful, stiff ("frozen") shoulder, unrelieved by other measures of treatment, relief of pain and freedom of movement may be accomplished with the systemic use of large doses of cortisone or corticotropin for only a few weeks while intensive physical treatment and exercises are employed. Local use of hydrocortisone infiltrated into the tissue around the shoulder is usually ineffective.

Pararheumatic Diseases.—There are several illnesses characterized by widespread fibrinoid degeneration of collagen fibers, commonly referred to as "diffuse collagen diseases." In this group are: disseminated lupus erythematosus, dermatomyositis, polyarteritis, and scleroderma. Although they are not true forms of arthritis or rheumatism, all these disorders have prominent rheumatic features. Chronic synovitis of the joints sometimes occurs.

Disseminated lupus erythematosus (*DLE*) is usually greatly benefited by proper administration of these hormones; indeed, cortisone and corticotropin have been the only agents which consistently exert significant control over this illness. Long remissions may follow the vigorous use of these hormones, but attempts to discontinue treatment are usually followed by relapse, and cortisone or corticotropin must be continued for an indefinite, long time. Although

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all or most of the numerous manifestations of the disease can usually be suppressed, the characteristic pathologic process is not arrested; if renal lesions have developed they persist, and often "L.E." cells persist in the blood of the treated persons.

Many patients, however, are kept alive and comfortable for years by continued treatment with cortisone or corticotropin, until failure of one of the vital organs results in death. Since DLE may be a fatal illness if untreated, it seems not only justified but essential to use one of these hormones as skillfully as possible for the effective control of patients severely ill from this malady.

Usually large daily doses, 100 mg. or more of cortisone, or 50 mg. or more of corticotropin, are required for long periods in order to accomplish suppression. In some cases as much as 1,000 to 2,000 mg. of cortisone acetate has been given intramuscularly daily to patients in an acute crisis.[34] Also in crisis, intravenous corticotropin or hydrocortisone in large doses may be necessary. Because of the common requirement for large doses and the frequent cardiac, renal, or pleural involvements, complications of treatment are numerous, and great care must be taken to control them. Many less serious but nevertheless troublesome side effects of these hormones must frequently be tolerated in order to use them for the life-prolonging benefit they produce.

Treatment of *dermatomyositis* produces variable results; in some patients the disease is suppressed for long periods, in other instances little benefit is obtained. Trial is justified whenever the disease is troublesome and progressive.

In patients with *polyarteritis* (including *periarteritis nodosa*), significant benefit frequently results from cortisone or corticotropin. In some patients treated for long periods, death has occurred from cardiac or renal failure, and at autopsy extensive arterial scars which occlude the lumen of vessels have been found. Such developments, thought to be hastened by hormone treatment, are unfortunate, but it is likely that if untreated, the disease would have terminated fatally from progressive inflammatory lesions. In the early stage of polyarteritis, excellent suppression can be accomplished, and can usually be sustained by continued treatment. Occasionally, remission may continue after discontinuance of the hormone.

Benefit of limited value has been observed in patients with *scleroderma.* Slow but definite softening and thinning of affected skin sometimes occurs if cortisone or corticotropin is used early in the illness and continued for long periods. In many advanced cases even large doses fail to effect practical benefit.

LIMITATIONS OF PRACTICAL USEFULNESS

This review of the use of cortisone, hydrocortisone, and corticotropin for various rheumatic diseases indicates the benefits which may be gained, and some of the troubles which may be encountered. Some undesired effects of these hormones may produce difficult problems, which limit practical usefulness in some patients.

In *acute* rheumatic disorders, the problems of hormone therapy are usually infrequent and mild. *The important complications and limitations of their practi-*

cal usefulness in rheumatic diseases are met most often in chronic illness. These problems and limitations are:

1. Although they have remarkable ability to suppress the activity of most inflammatory rheumatic diseases, cortisone and corticotropin have not the power to eliminate the pathologic process; hence *they cannot be expected to cure any disease.*

2. The value of hydrocortisone or cortisone administered directly or secreted under stimulation of corticotropin lasts only during administration of the hormones.

3. Hormone therapy does not repair damaged articular cartilage or bone, nor does it eliminate scarred connective tissue, hence *it cannot be expected to restore deformed arthritic joints or cardiac valves.*

4. *So many physiologic actions cannot be divorced from the antirheumatic effects* that undesired metabolic and hormonal results may outweigh the desired action.

5. *Corticotropin must be administered by injection*, a practical disadvantage when prolonged use is required in ambulatory patients.

6. Hydrocortisone acetate used intra-articularly has the same therapeutic limitations locally as in its systemic use, but undesired systemic effects are not encountered.

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INDICATIONS FOR USE OF HORMONES FOR RHEUMATIC DISEASE

The indications and contraindications for the use of cortisone and corticotropin cannot be precisely formulated. Opinions of various investigators do not entirely agree, and until experience is larger and extends over a longer time, unqualified recommendations cannot be made. It is clear that a patient with an *acute inflammatory* rheumatic disease may be considered a candidate for the use of cortisone or corticotropin, if the disease is worsening and other treatments have been unhelpful or inadequate. However, the merits of these hormones relative to other available treatment, such as salicylates for rheumatic fever and colchicine or phenylbutazone for acute gouty arthritis, are still debatable, so that the physician must make his own decision after careful consideration of all factors now known.

For *chronic* rheumatic disorders it is even more difficult to state precise indications. In general, noninflammatory osteoarthritis benefits so little that prolonged use of these hormones seems unjustified. All patients with rheumatoid arthritis may be expected to receive significant benefit from cortisone or corticotropin; the decision must be made of whether this potent treatment is warranted, and whether the benefits can be expected to outweigh troubles that may occur. No formula can be offered to answer this question. It is a matter of judgment based upon sound understanding of the known facts and upon experience. Many patients have such a mild form of rheumatoid arthritis that conservative treatment gives excellent results, and the more potent hormone treatment is not needed. In others with active disease, progressive in spite of all other therapy, it is desirable to employ cortisone or corticotropin as wisely

as possible to suppress the disease and minimize consequent incapacitation. In still other patients, disabled from previously active arthritis, the skillful use of cortisone or corticotropin combined with proper physical treatment may be of great value to accomplish quicker and greater restoration of joint and muscle function and thus materially aid in rehabilitation.

Intra-articular hydrocortisone acetate can be expected to have practical value in patients: (a) with only one or two troublesome joints, (b) who have good response to systemic treatment except for one or two joints which remain painful or disabling, (c) who cannot tolerate systemic therapy with steroids (hypertensive or diabetic patients, for example), (d) to aid rehabilitative physical or orthopedic treatment.

In some pararheumatic (collagen) diseases with grave prognosis (such as disseminated lupus erythematosus) the use of cortisone or corticotropin is justified even though troublesome complications may occur, for sometimes these serious illnesses may be suppressed only by the systemic use of these hormones.

CONTRAINDICATIONS

Absolute contraindications to the use of cortisone or corticotropin are few; more commonly relative contraindications must be weighed against the advantages to be expected. Hypercorticoadrenalism (Cushing's syndrome) is a definite contraindication; however, this relatively rare disease state seldom presents as a practical problem in patients with rheumatic diseases. In patients with acute psychoses, active tuberculosis or syphilis, or active peptic ulcer, these hormones should not be used. The history of previous psychosis or major emotional disturbances should make one hesitant; most psychoses that have occurred as complications during treatment have been in patients with such a history. Recently healed peptic ulcers may be reactivated, but an ulcer which has been completely healed for a period of one year or longer may not become active. Similar considerations are appropriate for long-arrested tuberculosis. Severe hypertension may be increased to a degree that is harmful, but in patients with only mild hypertension the hormones may provoke no trouble. Although severe diabetes mellitus may contraindicate the use of cortisone and corticotropin, in a mild diabetic state cautious use may be satisfactory. In renal insufficiency and severe congestive cardiac failure, these hormones may be dangerous, but in mild cardiac and renal disease trouble may not develop. In patients with severe osteoporosis, prolonged use of cortisone and corticotropin should be avoided. Bleeding tendencies may make the use of these hormones more hazardous; if they are employed in such conditions, vigilance should be exercised to recognize important hemorrhage, should it occur. During severe purulent infections it may be advantageous to discontinue the use of cortisone or corticotropin until the inflammatory process becomes satisfactorily localized. Seldom is there difficulty in healing of operative or accidental wounds in patients receiving these hormones in usual therapeutic doses.

Before hydrocortisone is unjected into a joint, in cases in which the diagnosis may be uncertain, it should be carefully determined that the joint inflammation is not caused by active infection in the joint structures.

PRECAUTIONS DURING USE OF HORMONES

The most important safeguards to the patient who receives cortisone or corticotropin are the physician's thorough understanding of the physiologic effects of these agents, and close surveillance throughout the treatment. Clinical checks should be made routinely, particularly regarding nervous tension, excitability, insomnia, personality changes, weight, pulse, blood pressure, edema, and menstrual disorders. Urinalysis for sugar weekly or biweekly and infrequent serum potassium determinations are advisable.

A diet adequate in essentials but restricted in caloric value will prevent generalized obesity; however, fatty jowls, round faces, and deposits of fat at the base of the neck posteriorly or above the clavicles and about the hips (especially in females) may occur even with these precautions. Hirsutism and acne may also occur, but if the dose of hormone is not high, these androgenic effects are usually only nuisances and do not prevent continuation of treatment. Rigid measures against edema are not needed in all patients. To avoid or to minimize edema, the diet should be low in sodium; medicines containing large amounts of sodium (sodium salicylate, sodium bicarbonate, and infusions of physiologic saline solution) should be avoided. Diuretics may be needed. It is unnecessary to administer potassium supplement routinely as prophylaxis against potassium deficiency because many patients do not require it. A wise course is to measure the serum potassium at intervals of a few weeks, and to look for symptoms or signs of potassium deficiency (marked weakness, flaccid paralysis, cardiac irregularities, hypotension, and characteristic electrocardiographic changes). Potassium chloride is a very effective supplement; doses of 1 or 2 Gm. daily usually correct deficiency and maintain normal tissue concentration. In patients who are febrile and gravely ill, loss of potassium is more likely to produce an important problem, and in them prophylactic use of potassium supplement is advisable.

Whether measures usually helpful for postmenopausal osteoporosis (high-protein diet, estrogen-androgen mixtures, and calcium or strontium salts) will be effective to prevent or correct the osteoporosis resulting from prolonged use of cortisone is now being studied. Recommendations cannot be made at this time.

Menstrual irregularities can usually be prevented or significantly reduced by appropriate doses of estrogenic substances given orally or intramuscularly.

Nervous tension, insomnia, unusual euphoria, or a sense of carefreeness should be regarded as unfavorable symptoms, for they often precede major excitement or depression. If these symptoms develop, the hormone should be discontinued or the dose should be sharply reduced.

Although infrequent, hypersensitivity to corticotropin may be of such importance that it is recommended that a test dose of 5 mg. be injected intramuscularly before starting to use this hormone. If no signs of anaphylactoid reaction occur within one or two hours, one need expect no difficulty from subsequent use of this hormone in therapeutic doses. Skin tests for sensitivity to corticotropin have been unreliable to indicate a hypersensitive state.

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After prolonged treatment with cortisone or hydrocortisone, unless abrupt cessation is required for a serious complication, it is preferable to withdraw the steroid very slowly. A reduction of only 5 to 10 mg. in the daily dose made at ten- to fourteen-day intervals is usually the best schedule. It is also advisable to administer stimulating doses of corticotropin at the end of prolonged cortisone therapy, to shorten the period of adrenal suppression.

Surgery in Cortisone-treated Patients.—Should it be necessary to perform a surgical operation on a patient who has had cortisone therapy within a few months prior to the surgery, it is highly important to administer supplemental cortisone or hydrocortisone for one or two days before the operation, on the day of operation, and for a few days thereafter. Although suppression of adrenal function may not result in adrenal insufficiency in usual circumstances, it may imperil life during the stress incident to a surgical operation. Usually tests of adrenal function are helpful, but normal results are not reliable indications that *great* stress can be met. It is, therefore, necessary to administer supplemental cortisone routinely as a prophylactic measure, when surgery is to be performed within three months (some investigators recommend twelve months) of cortisone treatment. Intravenous hydrocortisone (special alcohol solution) is particularly appropriate for use in postoperative patients receiving infusions.

It is a good precaution to provide the patient with a card that he should carry constantly, indicating that he is receiving cortisone. In case of accident, the medical attendants would know that precautions against adrenal insufficiency might be needed, and this information may be lifesaving.

OTHER STEROIDS STUDIED FOR ANTIRHEUMATIC EFFECT

After the remarkable antirheumatic effects of cortisone became known, it was natural that other steroids which had a chemical composition resembling cortisone should be tested for similar action. An early concern was the expense of cortisone. It was hoped that an inexpensive steroid could be made in large quantities. Later, the objective was primarily to find one that possessed potent antirheumatic action when administered orally, had little or no other physiologic action, and hence would produce few or no undesirable effects. In search for such an advantageous substance, a large number of steroids were synthesized and their pharmacologic value tested. For a while, pregnenolone was heralded as an effective cortisone substitute. However, when critically studied this steroid was found to possess no consistent antirheumatic effect.[35] All other steroids that have been tested have been found to be valueless as substitutes for cortisone or hydrocortisone.

Steroids which lack any one of the following characteristics have been found[36] to possess no antirheumatic properties:

1. OH at carbon 17.
2. Double bond between carbons 4 and 5.
3. Double-bonded O at carbon 3.
4. O or OH at carbon 11.
5. OH, or its salt, at carbon 21.

Various methods to augment the antirheumatic effects of cortisone and hydrocortisone have been tried. Simultaneous use of insulin was reported[37] to reduce the cortisone requirement; however, this effect has been inconsistent, and would be impractical even if it were helpful. Potassium para-aminobenzoate in large amounts together with cortisone has been reported to augment the antirheumatic effect, and thus lower the requirement for cortisone.[38] This method has been found unreliable by some investigators, but it is being studied further.

LOOKING AHEAD

Research progresses at an accelerated pace, and significant practical advances are being realized. Recently many steroid alterations have been developed by pharmaceutical chemists. Some of these have greater antirheumatic properties than the presently available steroids. One of these new steroids, 9 alpha fluoro hydrocortisone, has been found to have many times the antirheumatic potency of cortisone acetate, but it is unlikely that it will be of practical value because of the marked retention of sodium and water that it causes.[39,40]

Two newly synthesized steroids, metacortandracin and metacortandralone, have been found to have very potent antirheumatic potency.[41] The structure of metacortandracin has been announced to be delta 1, 4-pregnadiene-17 alpha, 21-diol-3, 11, 20-trione; that of metacortandralone is delta 1, 4-pregnadiene-11 beta, 17 alpha, 21-triol-3, 20-dione.[42] The structures of each of these new steroids are similar, and very similar to that of cortisone and hydrocortisone. Their administration to animals indicates that the eosinopenic response in adrenalectomized mice is three to four times the activity of cortisone or hydrocortisone, and that glycogen deposition in the liver and thymus involution are enhanced. Early clinical trials in patients with rheumatoid arthritis show that during continuous administration over a few months, antirheumatic potency is about three times that of hydrocortisone and four times that of cortisone and that some undesired effects are distinctly less frequently encountered and less severe.[41] If continued clinical investigations show these benefits can be consistently obtained, it seems reasonable that one of these new steroids may replace the currently used hydrocortisone and cortisone.*

A new salt of hydrocortisone shows promise of replacing hydrocortisone acetate for intra-articular use. Preliminary clinical trials indicate that, in some arthritics, tertiary-butyl-acetate of hydrocortisone injected into the joint cavity produces greater relief which lasts longer than that obtained from the same quantity of hydrocortisone acetate. In no cases is the local effect of the new derivative inferior to that of hydrocortisone acetate.

With advances such as these it seems reasonable that hormone treatment for rheumatic diseases will become better and more practical.

SUMMARY

Cortisone, hydrocortisone, and corticotropin may produce remarkable benefits in various types of rheumatic disorders. The manner of action of these

*Metacortandracin has now become a prescription drug (F.D.A. approved) and is now being used in many rheumatic disease centers in preference to hydrocortisone and cortisone acetate.

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potent hormones to produce antirheumatic effects is not known. The effects are temporary, suppressive but not curative, and there is no evidence that the ultimate course of a *chronic* rheumatic disease is favorably altered. There are potential dangers involved, because of which great care and definite precautions must be taken. The limitations of their usefulness have prevented the routine use of these agents in inflammatory rheumatic diseases. Indeed, the use of hormone therapy has become highly selective, for the purpose of realizing definite objectives.

The physician using these substances should realize their limitations and potential problems. Troubles must be expected to occur in some patients and the physician should be prepared to meet them. One must consider not only what may happen *during* their administration, but also what might occur *after* they are discontinued.

Although the practical usefulness of adrenal hormones has not fulfilled the high hopes originally held, despair is not warranted. Research continues and it is reasonable to anticipate that some current problems will be solved. The management of patients with rheumatic diseases should become more effective and on a firmer scientific basis.

REFERENCES

1. Freyberg, R. H., Traeger, C. H., Adams, C. H., Kuscu, T., Wainerdi, H. R., and Bonomo, I.: Effectiveness of Cortisone Administered Orally, Science **112**:429, 1950.
2. Boland, E. W., and Headley, N. E.: Compound F Used Orally in Patients With Rheumatoid Arthritis, J.A.M.A. **148**:981, 1952.
3. Hollander, J. L., Brown, B. M., Jr., Jessar, R. A., and Brown, C. Y.: Hydrocortisone and Cortisone Injected Into Arthritic Joints: Comparative Effects of, and Use of, Hydrocortisone as Local Antiarthritic Agent, J.A.M.A. **147**:1629, 1951.
4. Hollander, J. L.: Intra-articular Hydrocortisone in Arthritis and Allied Conditions, J. Bone & Joint Surg. **35A**:983, 1953.
5. Stevenson, C. R., Zuckner, J., and Freyberg, R. H.: Intra-articular Hydrocortisone (Compound F) Acetate, Ann. Rheumat. Dis. **11**:112, 1952.
6. Duff, I. F., Mikkelsen, W. M., Robinson, W. D., and Chatelin, N. H.: Intra-articular Hydrocortisone in Rheumatoid Arthritis, Internat. Rec. Med. **167**:515, 1954.
7. Freyberg, R. H., Traeger, C. H., Patterson, M., Squires, W., Adams, C. H., and Stevenson, C.: Problems of Prolonged Cortisone Treatment for Rheumatoid Arthritis, J.A.M.A. **147**:1538, 1951.
8. Wedgewood, R. J., Hawn, V., and Janeway, R. A. P.: Proc. Second Clin. ACTH Conf., Philadelphia, The Blakiston Company, **1**:108, 1951.
9. Rich, A. R., Cochran, T. H., and McGoon, D. C.: Marked Lipemia Resulting From Administration of Cortisone, Bull. Johns Hopkins Hosp. **88**:189, 1951.
10. Rose, B., Pare, J. A. P., Pump, K. K., and Stanford, R. C.: Preliminary Report on Adrenocorticotrophic Hormone (ACTH) in Asthma, Canad. M. A. J. **62**:6, 1950.
11. Ragan, C., Hawse, B. L., Plotz, C. M., Meyer, K., and Blunt, J. W.: Effect of Cortisone on Production of Granulation Tissue in the Rabbit, Proc. Soc. Exper. Biol. & Med. **72**:718, 1949.
12. Ragan, C.: Proc. Conf. on Effects of Cortisone, Rahway, N. J., 1951, Merck and Co., p. 54.
13. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: Effect of Hormone of Adrenal Cortex (17-Hydroxy-11-dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotrophic Hormone on Rheumatoid Arthritis: Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**:181, 1949.
14. Dobriner, K.: Adrenal Function in Rheumatoid Arthritis, Bull. Rheumat. Dis. **2**:5, 1951.
15. Patterson, M. B., Seigel, H. S., and Freyberg, R. H.: Recovery From Structural Changes Produced in Adrenal Glands of the Rat by Administration of Cortisone, Ann. Rheumat. Dis. **12**:217, 1953.
16. Barnes, A. R.: Effect of Cortisone and Corticotropin (ACTH) on Acute Phase of Rheumatic Fever: Further Observations, Am. J. Dis. Child. **82**:397, 1951.
17. Massel, B. F., and Warren, J. E.: Effect of Pituitary Adrenocorticotropic Hormone (ACTH) on Rheumatic Fever and Rheumatic Carditis, J.A.M.A. **144**:1335, 1950.

18. McEwen, C., Bunim, J. J., Baldwin, J. S., Kuttner, A. G., Baer, A. S., and Kaltman, A. J.: The Effect of Cortisone and ACTH on Rheumatic Fever, Bull. New York Acad. Med. **26**:212, 1950.
19. Thorn, G. W.: Medical Progress: Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:783, 824, 1950.
20. Greenstein, N. M.: Corticotropin in Rheumatic Carditis, Am. J. Dis. Child. **87**:694, 1954.
21. Bunim, J. J., Kuttner, A. G., Baldwin, J. S., and McEwen, C.: Cortisone and Corticotropin in Rheumatic Fever and Juvenile Rheumatoid Arthritis, J.A.M.A. **150**:1273, 1952.
22. Holbrook, W. P.: Comroe's Arthritis, ed. 5, Philadelphia, 1953, Lea & Febiger, p. 605.
23. Kuttner, A. G., Baldwin, J. S., McEwen, C., Bunim, J. J., Ziff, M., and Ford, D. K.: Effect of ACTH and Cortisone on Rheumatic Carditis, J.A.M.A. **148**:628, 1952.
24. Preliminary Report of Committee on Rheumatic Fever Study: Great Britain, Canada and United States, American Rheum. Assoc. Meeting, June, 1953.
25. Fischel, E. E., and Frank, C. W.: Use of Combined Therapy and Rebound Suppression in the Treatment of Rheumatic Fever, Program Am. Rheumatism Assoc., Interim Session, November, 1954.
26. Freyberg, R. H., Patterson, M., Adams, C. H., Durivage, J., and Traeger, C. H.: Practical Considerations of the Use of Cortisone and ACTH on Rheumatoid Arthritis, Ann. Rheumat. Dis. **10**:1, 1951.
27. Freyberg, R. H.: The Use of Cortisone in Rheumatic Diseases, Practitioner **167**:442, 1951.
28. Ward, L. E., Slocumb, C. H., Polley, H. F., Lowman, E. W., and Hench, P. S.: Clinical Effects of Cortisone Administered Orally to Patients With Rheumatoid Arthritis, Proc. Staff Meet., Mayo Clin. **26**:361, 1951.
29. Copeman, W. S. C., Savage, O., Dodds, C., Glyn, J. H., and Fearmley, M. D.: Management of Rheumatoid Arthritis With Prolonged Cortisone Administration, Brit. M. J. **1**:1109, 1954.
30. Joint Committee of Med. Res. Council and Nuffield Found.: A Comparison of Cortisone and Asparin in Treatment of Early Cases of Rheumatoid Arthritis, Brit. M. J. **1**:1223, 1954.
31. Bunim, J. J., Ziff, M., and McEwen, C.: Cortisone Therapy in Rheumatoid Arthritis: A Four Year Appraisal, Bull. Rheumat. Dis. **5**, 1954.
32. Bauer, W., Clark, W. S., Ropes, M. W., and Kulka, J. P.: Evaluation of Hormone Therapy in Rheumatoid Arthritis, Ann. Rheumat. Dis. **11**:305, 1952.
33. Boots, R. H., Yen, L. C., McMarrow, K. J., and Ragan, C.: Degenerative Joint Disease of Hip: Relief of Symptoms Following Cortisone Therapy, J.A.M.A. **147**:549, 1951.
34. Haserick, J. R., Corcoran, A. C., and Dustan, H. P.: ACTH and Cortisone in Acute Crisis of Systemic Lupus Erythematosus, J.A.M.A. **146**:643, 1951.
35. Freyberg, R. H., Adams, C. H., Stevenson, C., and Patterson, M.: Experiences With Pregnenolone and Other Steroids in Patients With Rheumatoid Arthritis, Symposium on Steroids in Experimental and Clinical Practice, Philadelphia, 1951, The Blakiston Company.
36. Kendall, E. C.: Adrenal Cortex and Rheumatoid Arthritis (Heberden Oration), Brit. M. J. **2**:1295, 1951.
37. Henderson, E., Gray, J. W., Weinberg, M., Merrick, E. Z., and Seneca, H.: Some Preliminary Observations on the Treatment of Rheumatoid Arthritis With Cortisone Plus Insulin, J. Clin. Endocrinol. **10**:800, 1950.
38. Wiesel, L. L., Barritt, A. S., and Strumpe, W. M.: Synergistic Action of Paraaminobenzoic Acid and Cortisone in Treatment of Rheumatoid Arthritis, Am. J. M. Sc. **222**:243, 1951.
39. Boland, E. W., and Headley, N. E.: Preliminary Clinical Trial With 9-Alpha Fluorohydrocortisone Acetate in Rheumatoid Arthritis, Program, Am. Rheumatism Assoc., Interim Session, November, 1954.
40. Ward, L. E., Polley, H. F., Slocum, C. H., and Hench, P. S.: Effects of Aldosterone and 9-Alpha fluorohydrocortisone Acetate Administered to Rheumatoid Patients: Preliminary Report, Proc. Staff Meet., Mayo Clin. **29**:649, 1954.
41. Bunim, J. J., Pecket, M. M., and Bollet, A. J.: Studies on Metacortandralone and Metacortandracin in Rheumatoid Arthritis, J.A.M.A. **157**:311, 1955.
42. Herzog, H. L., Nobile, A., Talksdorf, S., Charney, W., Hershberg, E. B., Perlman, P. L., and Pecket, M.: New Antiartiritic Steroids, Science. Submitted for publication.

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THE STRESS CONCEPT IN 1955

HANS SELYE, M.D., PH.D., D.SC., F.R.S. (C.), F.I.C.S. (HON.)

MONTREAL, QUEBEC

From the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal

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TWO monographs[1,6] and a series of "annual reports"[2-5] have been devoted to a detailed discussion of the literature on stress, a large section of which deals with conditions such as rheumatic diseases, hypertension, renal disease, arteriosclerosis, etc., which clearly fall into the group of maladies with which this JOURNAL is concerned. I limit myself here to a brief synopsis of the stress concept as it presents itself in 1955. I shall attempt to do this in the form of a survey based on the aforementioned publications, but outlining only their essence in a few pages. Thus, it will act as an introduction for those who would like to explore the relationships between stress and chronic disease, without overlapping too much with the series of special monographs and yearbooks, whose object is to serve as a detailed guide to the entire world literature.

Precursors of the Stress Concept.—Since man first used the word "disease" he had some, at least subconscious, inkling of the stress concept. The fact that a single term can be used to denote a great variety of individual maladies clearly indicates that they have something in common. They possess, as we would now say, some nonspecific features which permit one to distinguish disease from the condition of health. Yet, precisely because these manifestations are not characteristic of any one disease, they have received little attention in comparison with the specific ones. They were thought to be of lesser interest for, unlike the latter, they did not help to recognize the "eliciting pathogen" or lend themselves to any effective type of specific therapy.

Nevertheless, several early investigators have attempted to elucidate the mechanisms involved in such nonspecific reactions. Since our knowledge of the nervous system antedates, by far, the development of modern endocrinology, it is understandable that, among the two great integrating systems of the body, the nervous and the hormonal systems, the former was the first to be examined from this point of view. Ricker, Speransky, Reilly, Hoff, and many others have gathered important data concerning the role of the nervous system in such nonspecific reactions as fever, polymorphonuclear leukocytosis, inflammation, etc. In the domain of what may be called "physiologic stress," W. Cannon's studies helped us to understand the part played by the sympathetic nervous system and its humoral effector substances.

Furthermore, quite independently, a great deal of progress has been made in the study of pituitary and adrenocortical hormones by chemists, physiologists, and clinicians, too numerous to mention by name.

All the knowledge acquired as a result of these early investigations was indispensable for the eventual formulation of the stress concept, whose leading motive is one of unification. Additional experiments had to be performed, however, to show that the many nonspecific responses of individual target organs are closely integrated and actually represent part of a single biologic response, the general adaptation syndrome (G-A-S). These investigations, which will be outlined later, made it evident that the "stress pattern" of reaction plays an integral part in the most varied physiologic, pathologic, and pharmacologic phenomena.

The Concept of Stress.—By a series of experiments on animals, it was demonstrated in 1936 that the organism responds in a *stereotypical* manner to a variety of widely different factors, such as: infections, intoxications, trauma, nervous strain, heat, cold, muscular fatigue, or x-irradiation. The specific actions of all these agents are quite different. Their only common feature is that they place the body in a state of general (systemic) stress. Hence, we concluded that the stereotypical response, which is superimposed upon all specific effects, represents the somatic manifestations of nonspecific "stress" itself.

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But what is *nonspecific "stress"*? The term had long been used in physics to denote the interaction between a force and the resistance opposed to it. For instance, pressure and tension can put inanimate matter under stress. The aforementioned nonspecific response was thought to represent the biologic equivalent of such physical stress. The term has now been generally accepted in this sense not only in English, but—since attempts to translate "stress" led to much confusion—also in most other languages.

The Concept of the G-A-S.—The most outstanding manifestations of this stress-response were: *adrenocortical enlargement* with histologic signs of hyperactivity, *thymicolymphatic involution* with certain concomitant changes in the bloodcount (eosinopenia, lymphopenia, polynucleosis), and *gastrointestinal ulcers*, often accompanied by other manifestations of *damage or "shock."*

We were struck by the fact that, while during this reaction all the organs of the body show involutional or degenerative changes, the adrenal cortex actually seems to flourish on stress. We suspected this adrenal response to play a useful part in the systemic, nonspecific adaptive reaction, which we visualized as a "call to arms" of the body's defense forces and named the "alarm reaction."[7]

Subsequent studies showed that the alarm reaction is but the first stage of a much more prolonged *General Adaptation Syndrome* (G-A-S). The latter comprises three distinct stages, namely:

(1) *The alarm reaction* (A-R), in which adaptation has not yet been acquired.

(2) *The stage of resistance* (S-R), in which adaptation is optimal.

(3) *The stage of exhaustion* (S-E), in which the acquired adaptation is lost again.

The Mechanism of the G-A-S.—In order to elucidate the kinetics of this syndrome we proceeded as follows:

Rats were *adrenalectomized* and then exposed to stressor agents. This showed that in the absence of the adrenals, stress can no longer cause thymicolymphatic involution or characteristic blood count changes.[8]

When adrenalectomized rats were treated with the impure *cortical extracts* available at that time, it became evident that thymicolymphatic involution and the typical bloodcount changes could be produced by adrenal hormones even in the absence of the adrenals. Therefore, these changes were considered to be indirect results of stress mediated by corticoids.[8,9]

Conversely, the gastrointestinal ulcers and other manifestations of pure damage or shock were actually more severe in adrenalectomized than in intact animals and could be lessened by treatment with cortical extracts. It was concluded that these lesions are not mediated through the adrenal; in fact, they are actually combated by an adequate adrenocortical response to stressor agents.[8]

But what stimulates adrenocortical function during stress? In the course of the next year, we found that among many surgical interventions tried, only *hypophysectomy* prevented the adrenal response during the alarm reaction. Hence, we concluded that stress stimulates the cortex through an adrenocorticotrophic hormone, now known as ACTH.[10,11]

Then, pure cortical steroids became available, thanks to the classical investigations of Kendall and Reichstein. With these, we could show that administration of *mineralocorticoids* or *M-Cs* (such as desoxycorticosterone) produces experimental replicas of the so-called *hypertensive and inflammatory "rheumatic" diseases; notably, nephrosclerosis, hypertension, vascular lesions* (especially periarteritis nodosa and hyalin necrosis of arterioles)[12] as well as arthritic changes resembling, in acute experiments, those of rheumatic fever and, after chronic treatment, those of rheumatoid arthritis.[13] Yet, even very high doses of mineralocorticoids did not induce any noteworthy thymicolymphatic or blood count changes, such as were caused by cortical extracts.

Significantly, exposure of animals to certain nonspecific stressor agents (e.g., cold) produced marked adrenocortical enlargement and organ changes very similar to those elicited by the administration of mineralocorticoids.[14] Still, many investigators doubted that secretion of M-Cs could be involved in the pathogenesis of disease, since the very existence of natural, endogenous M-Cs was questioned. Indeed, until quite recently some of the most eminent students of the adrenal advocated the "unitarian theory," which held that the gland secretes only one corticoid, so that a derangement in the balance between antagonistic cortical hormones would be impossible. This concept was definitely disproved by the isolation of *aldosterone* from both the tissue and the venous blood of the adrenals.[15]

Extracts rich in *glucocorticoids or G-Cs* (such as cortisol and cortisone), on the other hand, were highly potent in causing *thymicolymphatic* involution and in eliciting the characteristic blood count changes of the alarm reaction.

They also tended to inhibit the inflammatory "rheumatic-like" changes which can be elicited in animals by mineralocorticoids. Thus, in many respects, the two types of corticoid hormones antagonize each other.[9,1]

Another interesting activity of the corticoids, discovered at about this time, is their singular effect upon the *central nervous system* of animals. A variety of steroids, among which figured both G-Cs (e.g., cortisone) and M-Cs (e.g., DCA), as well as other steroid hormones, and hormone metabolites (e.g., pregnanediol, pregnanedione), proved to possess the property of causing a state of great excitation and confusion, followed by marked depression of all reflex activities and, eventually, deep anesthesia.[16] This observation raised the question of whether a pronounced increase in the activity of endogenous corticoids could be responsible for certain nervous and emotional accompaniments of exposure to stress. After the introduction of cortisone into clinical therapy, it became evident that, in man, this hormone can also exert a powerful effect upon the central nervous system. In animals, both G-Cs and M-Cs exhibit this effect; hence we shall have to watch for it as soon as patients will be treated with large doses of aldosterone.

The terms "glucocorticoids" and "mineralocorticoids" emphasize the salient metabolic actions of these substances; from a clinical point of view, however, their effects upon inflammation are perhaps of even greater interest. Since the glucocorticoids inhibit inflammation, while the mineralocorticoids enhance it, the G-Cs may appropriately be called "*antiphlogistic corticoids*" or "*A-Cs*" and the M-Cs "*prophlogistic corticoids*" or "*P-Cs*," when they are discussed with reference to their effects upon inflammation. It remains to be seen, however, whether G-C and A-C (or M-C and P-C) activities necessarily run parallel in all steroid compounds, including those (like aldosterone) which have not yet been fully examined for these effects.

Inflammatory granulomas, especially those produced in the vicinity of joints by the local application of irritants (e.g., formalin, mustard powder), as well as certain allergic reactions, are likewise aggravated by P-Cs and inhibited by A-Cs. Apparently, the response of the adrenal cortex is most important not only in defense against systemic stress (affecting the whole organism), but also in the manifold topical defense reactions which occur upon exposure to *local stress* (e.g., bacterial or chemical irritants, response of a "shock organ" to an allergen).[17,1] These findings helped to formulate the concept of the Local Adaptation Syndrome (L-A-S) to be discussed later (cf. p. 588).

In this connection, the hormone sensitivity of certain so-called "*anaphylactoid inflammatory reactions*" is of special interest. Actually, our attention had first been called to a possible relationship between the adrenal cortex and inflammation by an incidental observation on rats given parenteral injections of egg white. It was found that the rat is naturally hypersensitive to egg white, and responds to the intraperitoneal or intravenous administration of this substance by an acute serous inflammation of the paws and snout. This inflammatory response was greatly aggravated in adrenalectomized animals (presumably because they could not defend themselves by the endogenous production of A-Cs). On the other hand, it was prevented by treatment with systemic stressors, directly in proportion to the adrenocortical enlargement they produced (presumably, as a result of excess A-C secretion).[11] Subsequently, it could be shown that cortisone and ACTH inhibit, while certain crude anterior-pituitary preparations and desoxycorticosterone aggravate, this anaphylactoid type of acute inflammation.[18]

Curiously, our *crude anterior pituitary extracts* also duplicated most of the aforementioned actions of P-Cs upon the *cardiovascular system, the blood pressure, the connective tissue (inflammation), and the kidneys*.[19,9] The hypophyseal

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preparations which we used were definitely corticotrophic, in that they enlarged the adrenal cortex, but they were particularly rich in the so-called "growth hormone" or *somatotrophic hormone* (*STH*). This made it difficult to interpret early experiments, in which such crude extracts were used, because we were unable to distinguish clearly between the effects of ACTH and STH. However, as soon as purified ACTH was available, it became evident that the aforementioned pathogenic actions of the crude anterior-pituitary preparations could not be due to their ACTH content, since even the highest tolerable doses of the pure corticotrophic hormone failed to duplicate their predominant P-C effects. On the other hand, overdosage with purified STH caused cardiovascular and renal lesions, virtually identical to those previously observed in animals treated with P-Cs. It was then concluded that, probably, the characteristic actions of crude anterior-pituitary preparations were mainly due to their STH content. It remains to be seen to what extent STH acts indirectly by stimulating the P-C production of the adrenal cortex, or directly by sensitizing the peripheral tissues to P-Cs. Preliminary observations suggest that the last-mentioned mechanism is more important, although both may be implicated.[20] This point is not yet settled.

From the internist's point of view, perhaps the most interesting role of STH in the adaptation syndrome is that it can effectively *combat catabolism and susceptibility to infections*. Animals heavily overdosed with ACTH or A-Cs, tend to lose a great deal of weight. Eventually they die, almost always as a result of generalized septicemia, caused by normally saprophytic microorganisms. In rats, the lung tissue appears to be singularly predisposed to such infections. Under these conditions, adequate doses of STH prevent the loss of body weight as well as the excessive microbial proliferation.[21] It remains to be seen to what extent these actions of STH will prove to be of value in the management of infections in man, but experiments on rats have already demonstrated the great influence of adaptive hormones upon resistance to the human type of tuberculosis. Normally the rat is virtually resistant to tuberculosis bacilli; it may be rendered sensitive by ACTH or A-Cs and this sensitivity can, in turn, be abolished by STH.[22,23]

Conditioning of Hormone Actions.—As work along these lines progressed, it became increasingly more obvious that the activity of the hormones produced during stress depends largely upon a variety of "conditioning factors." Both the production of the "adaptive hormones" and their effect upon individual target organs proved to be greatly influenced by heredity, age, previous exposure to stress, the nutritional state, etc. Thus, for instance, the production of corticotrophic hormone by the pituitary is enhanced by a high-protein diet, while the action of M-Cs upon most target organs is augmented by excess sodium.[9]

Stress itself is perhaps the most effective and most common factor capable of conditioning the actions of adaptive hormones. Thus systemic stress augments the antiphlogistic, lympholytic, catabolic, and hyperglycemic actions of A-Cs, while the salient effect of the adaptive hormones, that of modifying the course of inflammation, naturally cannot manifest itself unless some topical stressor first elicited a phlogistic response.

Ingle[24] introduced the concept of the "permissive actions" of corticoids. This term implies that the adrenal hormone does not affect a target of stress itself, although it permits a stressor to act upon it. Furthermore, allegedly the presence or absence of a permissive factor can only allow or disallow a reaction, but is unable to vary its intensity. To illustrate this concept one might compare the production of light by an electric lamp to the biologic reaction and the switch to the "permissive factor." The switch cannot produce light, nor regulate the degree of its intensity, but unless it is turned on, the lamp will not function. Correspondingly, the functional signs—generally considered to be characteristic of corticoid overproduction during stress—would not result from any actual increase in corticoid secretion, but from the extra-adrenal actions of the stressors themselves. The presence of corticoids would be necessary only in a "supporting capacity" to maintain the vitality and reactivity of tissues.

Actually, it is precisely in the specific and not in the nonspecific stress reactions that the corticoids play a purely "permissive role" of this type. Here they are necessary only to prevent stress and collapse, thus keeping the tissues responsive. For instance, adrenalectomized rats will not respond to injected STH with somatic growth, or to sexual stimulation with mating, without a minimal maintenance corticoid treatment. These reactions are in fact not characteristic of the corticoids and could not be duplicated, in the absence of the specific stimulus, even with the highest doses of corticoids. The characteristic functional signs of A-C overproduction which we see in the alarm reaction (e.g., atrophy of the lymphatic organs, catabolism, inhibition of inflammation) are also impeded by adrenalectomy and restored even by mere maintenance doses of A-Cs in the presence of stress, which sensitizes or "conditions" the tissues to them. However—unlike specific actions—these nonspecific effects can also be duplicated in the absence of any stressor if large doses of A-Cs are given (cf. "Fourth Annual Report on Stress," pp. 78-85).

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The importance of such conditioning influences is particularly striking in the regulation of stress reactions, because, in the final analysis, they are the factors which can actually determine whether exposure to a stressor will be met by a physiologic adaptation syndrome, or cause "diseases of adaptation." Furthermore, in the latter instance, these conditioning factors can even determine the selective breakdown of one or the other organ. We are led to believe that differences in predisposition, due to such factors, might explain why the same kind of stressor can cause diverse types of "diseases of adaptation" in different individuals.

Incidentally, it was only on the basis of such experiments that the mechanism through which stress affects the adrenal cortex could be clarified. We noted that stressors such as "formaldehyde, which caused marked adrenal hypertrophy in the normal, but not in the hypophysectomized animal, remained without effect (upon the adrenal), even if the adrenal cortex was prevented from undergoing atrophy by the administration of pituitary extract. The effect of such a drug on the adrenal appears to be an indirect one due to pituitary stimulation."[10]

The Concept of the Local Adaptation Syndrome (*L-A-S*).—It had long been known that many local responses to injury are nonspecific; it had been noted, for instance, that a variety of "topical stressors" (burns, microbes, drugs) share the power of producing nonspecific tissue damage and/or inflammation. However, it is only recently that the close relationship between the systemic and local types of nonspecific reactions has been more clearly established. While the characteristic response of the body to systemic stress is the G-A-S, characterized by manifold morphologic and functional changes throughout the organism, topical stress elicits a "Local Adaptation Syndrome" (L-A-S), whose principal repercussions are confined to the immediate vicinity of the eliciting injury. They consist, on the one hand, of degeneration, atrophy, and necrosis, on the other of inflammation, hypertrophy, hyperplasia, and, under certain conditions, neoplasia. (Cf. "Fourth Annual Report on Stress," p. 48.)

L-A-S and G-A-S.—At first sight, there appears to be no striking similarity between the systemic and the local reaction type. A patient in traumatic shock furnishes a characteristic example of the G-A-S and, in particular, of its earliest stage, the "shock phase" of the general alarm reaction. An abscess formed around a splinter of wood represents a typical example of the L-A-S and, in

particular, of its "stage of resistance," during which the defensive inflammatory phenomena predominate. On the surface, these two instances of disease reveal no striking similarities and yet, more careful study shows them to be closely related.

The experimental observations which led us to these conclusions have been described elsewhere.[25,26] Let us restate here, however, that, among other things, the G-A-S and the L-A-S are thought to be interrelated because:

(I) both are nonspecific reactions, comprising damage and defense;

(II) both are triphasic, with typical signs of "crossed resistance" (or, depending upon the stressors used, "crossed sensitization"), during the second stage;

(III) both are singularly sensitive to the so-called "adaptive hormones" (ACTH, STH, corticoids);

(IV) If the two reactions develop simultaneously in the same individual, they greatly influence one another; that is, systemic stress markedly alters tissue reactivity to local stress and *vice versa*.

The Concept of the Diseases of Adaptation.—Thus we arrived at the conclusion that the pathogenicity of many systemic and local stressor agents depends largely upon the function of the hypophysis-adrenocortical system. The latter may either enhance or inhibit the body's defense reactions against stressors. We think that derailments of this adaptive mechanism are the principal factors in the production of certain maladies which we consider, therefore, to be essentially *diseases of adaptation.*

It must be kept in mind that such diseases of adaptation do not necessarily become manifest during exposure to stress. This is clearly demonstrated by the observation that temporary overdosage with desoxycorticosterone can initiate a self-sustaining hypertension, which eventually leads to death, long after hormone administration had been discontinued. Here, we speak of "metacorticoid" lesions. The possibility that a temporary excess of endogenous aldosterone could induce similar delayed maladies deserves serious consideration.

Among the derailments of the G-A-S which may cause disease, the following are particularly important:

(1) An *absolute excess or deficiency* in the amount of adaptive hormones (e.g., corticoids, ACTH, STH) *produced* during stress.

(2) An absolute excess or deficiency in the amount of adaptive hormones *retained* (*or "fixed"*) by their peripheral target organs during stress.

(3) A *disproportion* in the relative secretion (or fixation) during stress of various antagonistic adaptive hormones (e.g., of ACTH and A-Cs, on the one hand, and of STH and P-Cs, on the other).

(4) Production by stress of metabolic derangements, which abnormally alter the *target organ's response* to adaptive hormones (through the phenomenon of "conditioning").

(5) Finally, one must not forget that, although the hypophysis-adrenal mechanism plays a prominent role in the G-A-S, *other organs* which participate in the latter (e.g., nervous system, liver, kidney) may also respond abnormally and become the cause of disease during adaptation to stress.

Summary of Observations.—To summarize, one might say that all agents which act upon the body or any of its parts exert dual effects:

(1) *Specific actions*, with which we are not concerned in this review, except in so far as they modify the nonspecific actions of the same agents.

(2) *Nonspecific or stressor effects*, whose principal pathways (as far as we know them today) are illustrated in Fig. 1.

The *stressor* acts upon the target (the body or some part of it) directly (thick arrow) and indirectly through the pituitary and adrenal.

Through some *unknown pathway* (labeled by a question mark), the "first mediator" travels from the directly injured target area to the *anterior pituitary*. It notifies the latter that a condition of stress exists and thus induces it to discharge ACTH.

It is quite possible that this "first mediator" of hormonal defense is not always the same. In some instances, it may be an adrenaline discharge, in others a liberation of histamine-like toxic tissue metabolites, a nervous impulse, or even a sudden deficiency in some vitally important body constituent (such as glucose or an enzyme).

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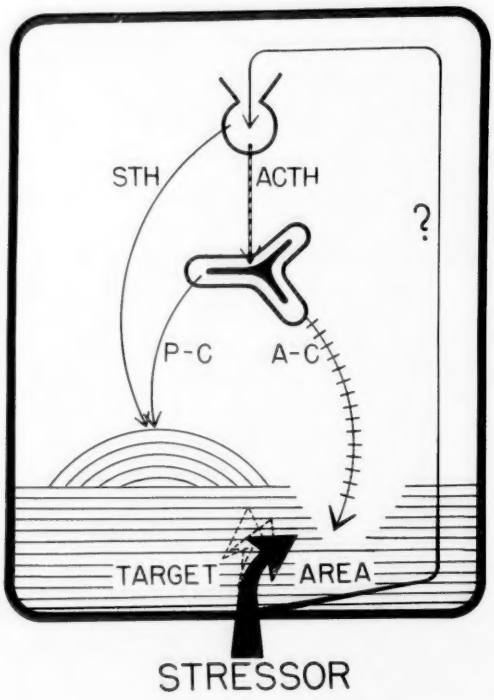

Fig. 1.—After Selye.[6]

ACTH stimulates the *adrenal cortex* to discharge corticoids. Some of these, the *prophlogistic corticoids* (*P-C*), stimulate the proliferative ability and reactivity of connective tissue; they enhance the "inflammatory potential." Thus, they help to put up a strong barricade of connective tissue through which the body is protected against further invasion by the pathogenic stressor agent.

However, under ordinary conditions, ACTH stimulates the adrenal much more effectively to secrete *antiphlogistic corticoids* (*A-C*). These inhibit the ability of the body to put up granulomatous barricades in the path of the invader; in fact, they tend to cause involution of connective tissue with a pronounced depression of the inflammatory potential. Thus they open the way to the spreading of infection.

It is not yet known whether ACTH always stimulates the adrenal to produce the various corticoids in the same proportion and always with a great predominance of A-Cs. Certain recent experiments[27] suggest that, depending upon conditions, ACTH may cause the predominant secretion of one or the other of the steroid hormones. However, be this as it may, the *somatotrophic hormone* (STH) of the pituitary increases the inflammatory potential of connective tissue, very much as the P-Cs do; hence, it can sensitize the target area to the actions of the latter.

It is possible that the hypophysis also secretes some special corticotrophin which induces the adrenal to elaborate predominantly P-Cs; indeed, STH itself may possess such effects, but this has not yet been proved. In any event, even if ACTH were the only corticotrophin, the actions of the corticoids produced under its influence can be vastly different, depending upon "conditioning factors" (such as STH), which specifically sensitize the target area for one or the other type of corticoid action. Actually, conditioning factors could even alter the response to ACTH of the adrenal cortex itself, so that its cells would produce more A-Cs or P-Cs. Thus, during stress, one or the other type of effect can predominate.

The fundamental reaction-pattern to topical stressors is a local adaptation syndrome with inflammation; to systemic stressors, the general adaptation syndrome. Various modifications of these two basic responses constitute the essence of most diseases.

Outlook Suggested by These Observations.—Pasteur, Koch, and their contemporaries introduced the concept of specificity into medicine, a concept which proved to be of the greatest heuristic value up to the present time. Each individual, well-defined disease, they held, has its own specific cause. It has been claimed by many that Pasteur failed to recognize the importance of the "terrain," being too preoccupied with the pathogen (microorganism) itself. His work on induced immunity shows that this is incorrect. Indeed, allegedly at the end of his life he said: "*Le microbe n'est rien, le terrain est tout.*"

The theory which directed the most fruitful investigations of Pasteur and his followers was that the organism can develop specific adaptive reactions against individual pathogens and that by imitating and complementing these, whenever they are short of optimal, we can treat many of the diseases which are due to specific pathogens.

To my mind, the General Adaptation Syndrome represents, in a sense, the negative counterpart, or mirror image, of this concept. It holds that many diseases have no single cause, no specific pathogen, but are largely due to nonspecific stress, and to pathogenic situations which result from inappropriate responses to such nonspecific stress.

This blueprint of the pathways through which stress acts may be partly incorrect; it is certainly quite incomplete. But in it we have a basis for the objective scientific dissection of such time-honored, but hitherto rather vague, concepts as the role of "reactivity," "constitution and resistance," or "nonspecific therapy," in the genesis and treatment of disease.

If I may venture a prediction, I would like to reiterate my opinion *that research on stress will be most fruitful if it is guided by the theory that one must*

learn to imitate—and, if necessary, to correct and complement—the body's own autopharmacologic efforts to combat the stress factor in disease.

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REFERENCES

1. Selye, H.: Stress. The Physiology and Pathology of Exposure to Stress, Montreal, 1950, Acta, Inc.
2. Selye, H.: First Annual Report on Stress, Montreal, 1951, Acta, Inc.
3. Selye, H., and Horava, A.: Second Annual Report on Stress, Montreal, 1952, Acta, Inc.
4. Selye, H., and Horava, A.: Third Annual Report on Stress, Montreal, 1953, Acta, Inc.
5. Selye, H., and Heuser, G.: Fourth Annual Report on Stress, Montreal, 1954, Acta, Inc.
6. Selye, H.: The Story of the Adaptation Syndrome, Montreal, 1952, Acta, Inc.
7. Selye, H.: A Syndrome Produced by Diverse Nocuous Agents, Nature **138**:32, 1936.
8. Selye, H.: Thymus and Adrenals in the Response of the Organism to Injuries and Intoxications, Brit. J. Exper. Path. **17**:234, 1936.
9. Selye, H.: The General Adaptation Syndrome and the Diseases of Adaptation, J. Clin. Endocrinil. **6**:117, 1946.
10. Selye, H., and Collip, J. B.: Fundamental Factors in the Interpretation of Stimuli Influencing Endocrine Glands, Endocrinology **20**:667, 1936.
11. Selye, H.: Studies on Adaptation, Endocrinology **21**:169, 1937.
12. Selye, H., and Pentz, I.: Pathogenetic Correlations Between Periarteritis Nodosa, Renal Hypertension and Rheumatic Lesions, Canad. M. A. J. **49**:264, 1943.
13. Selye, H., Sylvester, O., Hall, C. E., and Leblond, C. P.: Hormonal Production of Arthritis, J.A.M.A. **124**:201, 1944.
14. Selye, H.: On the Production of Maligmant Hypertension by Chronic Exposure to Various Damaging Agents, Rev. canad. biol. **2**:501, 1943.
15. Simpson, S. A., Tait, J. F., Wettstein, A., Neher, R., v. Euw, J., and Reichstein, T.: Isolierung eines neuen kristallisierten Hormons aus Nebennieren mit besonders hoher Wirksamkeit auf den Mineralstoffwechsel, Experientia **9**:333, 1953.
16. Selye, H.: Correlation Between the Chemical Structure and the Pharmacological Actions of the Steroids, Endocrinology **30**:437, 1942.
17. Selye, H.: Further Studies Concerning the Participation of the Adrenal Cortex in the Pathogenesis of Arthritis, Brit. M. J. **2**:1129, 1949.
18. Selye, H.: Effect of ACTH and Cortisone Upon an Anaphylactoid Reaction, Canad. M.A.J. **61**:553, 1949.
19. Selye, H.: Role of the Hypophysis in the Pathogenesis of the Diseases of Adaptation, Canad. M.A.J. **50**:426, 1944.
20. Selye, H.: The Rôle of Somatotrophic Hormone (STH) in the Production of Malignant Nephrosclerosis, Periarteritis Nodosa and Hypertensive Disease, Brit. M.J. **1**:263, 1951.
21. Selye, H.: The Influence of STH, ACTH, and Cortisone Upon Resistance to Infection, Canad. M.A.J. **64**:489, 1951.
22. Lemonde, P., Panisset, M., Dobija, M., and Selye, H.: Protection by Somatotrophic Hormone (STH) Against Experimental Tuberculosis, J. Clin. Endocrinol. **12**:973, 1952.
23. Lemonde, P., Panisset, M., Dobija, M., and Selye, H.: Influence de la somatotrophine sur la tuberculose expérimentale chez le rat et la souris, Ann. endocrinol. **13**:897, 1952.
24. Ingle, D. J.: III. Hormones and Metabolism. Parameters of Metabolic Problems, Recent Progress Hormone Research **6**:159, 1951.
25. Selye, H.: The Local Adaptation Syndrome (L-A-S), XIX Congr. internat. physiol. **31** août-4 sept., p. 750, Montréal, 1953.
26. Selye, H.: On the Mechanism Through Which Hydrocortisone Affects the Resistance of Tissues to Injury (an Experimental Study With the "Granuloma-Pouch Technique"), J.A.M.A. **152**:1207, 1953.
27. Hechter, O.: The Adrenocortical Secretory Product. In: The Mechanism of Inflammation. An International Symposium, p. 21, Montreal, 153, Acta, Inc.

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Editorials

MODERN CONCEPTS OF EPIDEMIOLOGY

Modern practices have restored to epidemiology the concepts and functions which stem from the original sense of the word. It was through years of special application to the study and control of communicable diseases that its usage became restricted. The change in meaning over the years and the variety of opinion as to its meaning today are reflected in the following definitions: *Webster's New Collegiate Dictionary* (1950) limits epidemiology to the study of epidemics as follows: "the medical science treating of epidemics." *Stedman's Practical Medical Dictionary* (1946) shows an extension of the meaning beyond epidemics per se to all epidemic diseases: "the science of epidemics and epidemic disease." Greenwood, in 1935, subscribed to a further extension: "the study of disease, *any* disease, as a mass phenomenon." Maxcy in Dorland's dictionary and in Rosenau: *Preventive Medicine and Hygiene*[1] gives a definition which is generally accepted among epidemiologists today: "that field of medical science which is concerned with the relationship of the various factors and conditions which determine the frequencies and distributions of an infectious process, a disease, or a physiologic state in a human community."

Literally, the roots of the word mean "on, upon or to the people." Thus, epidemiologic principles and methods are being applied not only to the communicable diseases but also to other disorders on or upon the people: heart disease,[2] essential hypertension,[3,4] mental disorders,[5,6] nutritional deficiencies,[7] accidents,[8] mottled enamel,[9] congenital defects,[10] and other disorders which affect populations.

These disorders are the result of imbalance between agents of disease and man; the extent of the imbalance depends upon the characteristics of the agents and those of man; and these characteristics are largely governed by the conditions of the environment. Thus, within the agent, the host and the environment are all the conditions and circumstances which initiate and perpetuate a disease process. The process actually begins before man himself is involved. There are genetic and environmental influences which determine whether or not man will come in contact with disease agents (infectious or noninfectious) and once man and agent meet, similar influences may determine the outcome of the interaction. There are two related processes, one taking place in the environment before man is actually affected and the other the process of interaction of man and disease agent (the course of the disease in man). For example, malaria has its origin in

a process in the environment, which depends on the presence of the *Anopheles* mosquito, climatic conditions, and the availability of the causative agent. Prevention and control depend on the knowledge of this process before man is affected. Similarly, lead poisoning results from an environmental process which permits the disease agent (lead) to come in contact with man. This process must be interrupted to prevent the disease process in man.

The combination of these processes (i.e., the one in the environment and the one in man, beginning with the first initiating forces wherever they may be, through the resulting changes which take place in man and until equilibrium is reached or defect, disability, or death ensues) may be termed, especially for epidemiologic and preventive purposes, the natural history of a disease.[11,12]

The body of knowledge about the natural history of any disease is the result of facts and observations, assembled from many fields of science, being integrated with those relating to the occurrence of disease according to age, race, sex, occupation, heredity, personal habits, and other host characteristics, and the details of the physical, social, economic, and biologic environment. It is a function of epidemiology to collect and organize such data from diverse sources in order to describe the natural history of disease. Such is *descriptive* epidemiology. Epidemiologic description differs from clinical description in the basic *unit* of observation. In the latter, the unit is an individual and the clinical reaction is described as it is manifest in that individual and others so affected. For the epidemiologic description, the unit is an aggregation of individuals and the description includes the host and environmental characteristics of both the affected and the nonaffected in the population concerned.

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That epidemiology is also a constructive or analytical science was first expressed by Frost, the greatest of American epidemiologists: "Epidemiology is something more than the total of its established facts. It includes their orderly arrangement into chains of inference which extend more or less beyond the bounds of direct observation. Such of these chains as are well and truly laid guide in investigation to the facts of the future. Those that are ill laid fetter progress."[13]

The methods of modern epidemiology (constructive epidemiology), as applied to the study of the mass phenomena of health and disease, are based upon scientific principles which are common to other scientific disciplines as well. The epidemiologic method comprises a continuum of several orderly steps. In the investigation of any aspect of health and disease, the method can be systematized into an approach comprising five steps which conform to those of long proved value in the investigation of epidemics. They are:

1. *Definition of the nature and significance of the problem.* In any epidemiologic investigation this comprises a definition of terms, the clarification of objectives, and the formulation of specific questions. In a suspected epidemic, defining the problem means the verification of diagnosis of reported cases and the careful comparison of present with usual occurrence to determine if an epidemic exists.

2. *Critical appraisal of existing information* on the subject to separate fact and hypothesis and to define gaps in knowledge. This is more than the conven-

tional review of the literature. It is critical evaluation of existing knowledge. In the solution of an epidemic, this step serves to orient the epidemic as to time, place, and person, based on existing cases and the environmental circumstances.

3. *Formulation of hypotheses* based upon critical evaluation. Carefully stated hypotheses provide the basis for the design and details of the investigation. In epidemics, this is a preliminary working hypothesis for immediate action and to aid in further investigation.

4. *Testing of hypotheses.* This comprises the design and execution of the investigation with careful attention to sample selection, controls, methods of collecting, recording, and analyzing the data. In epidemics, it is the search for unreported cases and the detailed investigation of each case and the attendant circumstances.

5. *Conclusions and practical application.* This includes the evaluation of the outcome of the investigation in terms of the original questions and stated hypotheses. In completing an epidemic study this means evaluation in terms of present control and future prevention.

These five steps are the application of the scientific method to problems pertaining to aggregations of individuals.*[14] They are not unique to epidemiology but are applicable to clinical and laboratory problems as well. "The unity of science is in its method" (Pearson[15]). The scientific method is the same wherever it is applied. The differences are in the material (people, microorganisms, chemicals, etc.); the focus of the observation (single units or aggregations); and the locale (bedside, clinic, laboratory, field).

It is indeed clear from current usage that the definition of epidemiology has been extended far beyond its original sense as the doctrine or science of epidemics. It is certain that its scope is not limited to diseases in which epidemics are characteristic, since it is in conformity with good usage to consider the epi demiology of tuberculosis, for example. Furthermore, its scope is not limited to communicable disease because it is proper to speak of the epidemiology of cancer, of scurvy, of accidents. The extent of change in the meaning of epidemiology is borne out in the following generally accepted definition: This is a field of science which is concerned with the various factors and conditions which determine the occurrence and distribution of health, disease, defect, disability, and death among aggregations of individuals; it has application also to problems other than those of health and disease.

REFERENCES

1. Maxcy, K. F. (Editor): Rosenau: Preventive Medicine and Hygiene, ed. 7, New York, 1951, Appleton-Century-Crofts, Inc.
2. Dauber, T. R., Meadors, G. F., and Moore, E., Jr.: Epidemiological Approaches to Heart Disease: The Framingham Study, Am. J. Pub. Health **41**:279, 1951.
3. Clark, E. G., and Morsell, J. A.: An Epidemiologic Approach to the Study of High Blood Pressure, Am. J. Pub. Health **42**:542, 1952.

*An example of the application of these steps in the study of essential hypertension will be found in a series of papers to be published in a forthcoming issue of this Journal.

4. Symposium on Essential Hypertension: An Epidemiologic Approach. Recess Commission on Hypertension, Commonwealth of Massachusetts. Edited by the Division of Epidemiology of Columbia University School of Public Health, and the Bureau of Applied Social Research of Columbia University, Boston, 1951, Wright and Potter Printing Company.
5. Epidemiology of Mental Disorder, A Symposium, New York, 1950, Milbank Memorial Fund.
6. Gordon, J. E., O'Rourke, Ed., Richardson, F. L. W., Jr., and Lindemann, E.: The Biological and Social Sciences in an Epidemiology of Mental Disorder, Am. J. M. Sc. **223**:316 1952.
7. Gordon, J. E., and Le Riche, H.: The Epidemiologic Method Applied to Nutrition, Am. J. M. Sc. **219**:321, 1950.
8. Gordon, J. E.: The Epidemiology of Accidents, Am. J. Pub. Health **39**:504, 1949.
9. Gordon, J. E., and Hawkins, J. W.: Epidemiological Aspects of Mottled Enamel, Am. J. M. Sc. **199**:431, 1940.
10. Ingalls, T. H.: The Study of Congenital Anomalies by the Epidemiologic Method, New England J. Med. **243**:67, 1950.
11. Perkins, W. H.: Cause and Prevention of Disease, Philadelphia, 1938, Lea & Febiger.
12. Leavell, H. R., and Clark, E. G.: Textbook of Preventive Medicine, New York, 1953 McGraw-Hill Book Company, Inc.
13. Frost, W. H.: in Snow, John: On Cholera, New York, 1936, Commonwealth Fund, Introduction.
14. Clark, E. G., and Danbolt, N.: The Oslo Study of the Natural History of Untreated Syphilis, J. CHRON. DIS. **2**:311, 1955.
15. Pearson, K.: The Grammar of Science, London, 1949, Everyman's Library.

E. GURNEY CLARK, M.D.
Columbia University School of Public Health
New York, N. Y.

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RESEARCH IN THE RHEUMATIC DISEASES

It is the prerogative of the elderly members of a profession to offer criticism of their profession's work and methods. I am, therefore, most anxious that I should not be considered presumptuous in offering these comments. I would assure you that they are presented in no sense of carping criticism, but, rather, as a personal reaction to modern trends and techniques as applied to my own specialty.

The last ten years has seen an enormous upsurge of enthusiasm and endeavor in the field of the rheumatic diseases, and, indeed, probably more has been accomplished in understanding and treating these diseases in the last decade than ever previously in a century.

Research programs appear to fall into four broad groups thus:

1. *Basic Research Into the So-called "Collagen" Diseases.*—As one may readily understand, such pure scientific work is, for the moment, largely in the hands of biochemists, histopathologists, and physicists since the present problem is to understand the economy of collagen tissue and its elements. It is difficult to see just when and how the results of implanting the hind leg of a rat in its abdominal wall are to be applied to the treatment of patients suffering from rheumatoid arthritis. It may be argued that all technical advances have their theoretic and, for the moment, apparently unrelated academic origins. In the case I am discussing, however, an additional difficulty arises, namely, that the "collagen" diseases may not exist but may simply represent a nonspecific reaction on the part of unspecialized supporting tissue and substance to a great variety of stimuli.

2. *Research on the Pituitary and Adrenal Axis.*—The demonstration of the therapeutic possibilities of an adrenal cortical steroid, namely, cortisone, served as a starting point for an immense amount of work presently represented by cortisone, hydrocortisone, electrocortin, and ACTH in its many forms. It is, I think, true, however, that while the first application of this group of substances by Hench and his colleagues was to the treatment of the rheumatic diseases, the scope of this work has now grown to such proportions that its original therapeutic use has become progressively less absorbing to experimentalists. A number of factors are probably responsible, e.g.:

a. The recognition that no cure had been found.

b. The discovery that many other diseases responded as dramatically as the rheumatic group, if not more so, to the first exhibition of these steroids.

c. The realization that continued administration of the compounds was not without danger.

d. The attraction of building on a new foundation speculative theories concerning pathogenesis and physiologic mechanics.

e. The disinterest in the rheumatic group of diseases exhibited by those not specializing in that field.

Whatever the cause, research into the activity of adrenal steroids and their like seems to veer toward theoretical and experimental concepts and away from the path of its origin.

3. *Experimental Pharmacology.*—This is the field in which I am myself engaged but I hold no special brief for it. It is unscientific in approach and even unintelligent at times. It consists of painstakingly investigating all those compounds and their immediate and remote relations which appear or appeared to affect beneficially some aspect of the rheumatic diseases. It was while work of this kind was being done that the value of phenylbutazone was first suspected. Again, however, we have an example of deviation from our original task, and I and many other workers to whom I have spoken find we are devoting more and more time to screening compounds for edema-inhibiting and antiphogistic properties rather than for true antirheumatic activity. Such deviation is easy to excuse but not so easy to explain. It may be that it is the result of an effort, albeit subconscious, to conform to orthodox scientific standards rather than to continue the unorthodox "playing of hunches"—but I shall return to this in a moment.

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4. *Statistical Research.*—It has been said that statistical analysis is no substitute for intelligent evaluation; but nonetheless this constitutes one of the most popular forms of research at the present time. All manner of surveys are being conducted in every country with regard to the population incidence, occupational incidence, economic group incidence, climatic incidence, family incidence, sex incidence, age incidence, and a host of other incidences of rheumatic disease. These investigations may provide useful and even valuable information in their own limited way, but it is important to realize the great limitations in applying mathematical tests to biologic material. This is neither the time nor the place to develop this precise argument, but let me say this: All such analyses depend for their validity on the accuracy of the basic facts provided, and this is nowhere more monumentally difficult than when dealing with *Homo sapiens.*

The practice of medicine is still as much an art as a science, yet such devotion is shown to the scientific component that simple clinical observations are no longer acceptable unless they are cloaked in terms of pseudoscientific accuracy. Every week one reads papers in medical journals where writers quite seriously refer to ten out of twenty as 50 per cent. One sees small series of cases recorded and "statistically" analyzed where the standard deviation or differential is so great as to make the whole analysis worthless. The authors of these papers are not alone responsible, for many editors and editorial boards now insist on such analyses of results being included. Not long ago I sent a short paper to a reputable British journal. It was concerned with the results of some experimental pharmacologic work in some forty patients. I had a letter from the editor accepting the paper for publication but asking me to let him have a short statistical analysis for the end of the communication. This

he averred was insisted on by his "advisors." I pointed out that if his "advisors" would indicate to me how these results could be mathematically analyzed I should be eternally grateful to them. The paper was published without further comment.

We see this regrettable tendency throughout medicine at the present time. There is undoubtedly a vogue for expressing clinical opinions in terms of mathematical symbols which cloak the observations with an apparent degree of accuracy they do not contain.

Again, too, there is a tendency to regard the result produced by the laboratory technician as having greater accuracy than experienced clinical judgment. Most diagnostic tests depend on one reaction in health and a diametrically opposite one in some pathologic state. Is there any reason to expect that when we are clinically doubtful, the results of a test based on these concepts will be any less doubtful?

In conclusion, it seems to me just as likely that progress in the understanding and treatment of rheumatic disease will come from someone standing well back and surveying the whole problem as from someone peering through a powerful microscope at one small section of it. By all means let us research into colloid chemistry and peripheral antiphogistic corticoid conditioners; let us analyze our results and use our laboratories; but let us also remember the importance of looking at our patients and their diseases. Let us use all the scientific and mathematical methods available, but let us first be sure that our material is analyzable and calculable.

He who would appreciate a beautiful lawn will do so better by walking slowly over it than by studying a few sample blades of grass under a microscope.

JOHN P. CURRIE, M.B., CH.B., M.D.
Rheumatism Unit, Royal Infirmary
Glasgow, Scotland

THE PROBLEM OF CHRONICALLY ILL AND CUSTODIAL PATIENTS IN PUBLIC INSTITUTIONS

The Clinician's Viewpoint

The gradual accumulation of patients in the public hospitals who are in no immediate need of active medical care is severely affecting the effectiveness of many vitally important institutions and their ability to fulfill their primary missions. These people are often referred to as "custodial patients," a term which is not only a misnomer but, more than that, grossly misleading. "Custodial" would indicate that such hospital residents need nothing but domiciliary care, whereas the word "patient" still identifies them as those whose primary needs are medical services. The fact is that these are people who have little need for the medical services of a hospital. They could be best placed in homelike living arrangements which would fulfill their essential wants. No hospital is or should be designed to satisfy such nonmedical requirements.

A recent study[1] conducted by a New York University-Bellevue Medical Center research group, while done on a small sample, has convincingly brought out some of the main factors of this anomalous situation. This study, financed by the New York Foundation, found that an unselected group of ninety-five persons designated as "custodials" had spent more than a quarter of a million practically uninterrupted days in municipal hospitals. Even more startling was the conclusion that after a careful medical evaluation, only five of them were found to be medically in need of continued hospital care. In two others, the need for hospitalization was questionable. It was also found that a number would have had a better than fair chance to leave the hospital after intensive rehabilitation.

This study brings up the important question whether a hospital, which is primarily an institution of healing, teaching, and research, should weaken its efficiency by taking care of people whose needs are other than medical.

An accumulation of nonmedical problems adversely affects the hospital by: (1) Gradually changing its character to a domiciliary institution; (2) causing professional personnel to lose interest and ambition; (3) seriously impairing teaching and research programs; (4) uneconomically utilizing such essential services as operating rooms and laboratories; (5) overtaxing the professional staff with nonessential duties.

The best interest of these "custodial patients" is not served by keeping them in a hospital. They are compelled to live in a hospital atmosphere in which they do not belong. Not being actively ill, they require and receive little or no medical attention. They spend many years of their lives in an environment of pain, hopelessness, and death. A poor substitute for a home, indeed!

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It is easy to see that we are confronted with a complicated situation which affects both the hospitals and the needlessly hospitalized individuals. These problems, together with the constantly mounting cost of hospital services, compel us to take decisive steps toward radical improvements.

One of the first steps we must take toward such improvement is the clarification of the terms "chronically ill" and "custodial." Without engaging in purely academic discussion or semantics, we can say that the "chronically ill" patient is one whose treatment may take a long period of time, who is in need of continuous active medical care and/or rehabilitation, and who has a good chance to improve or recover. From this, it follows logically that a chronic disease hospital is, or should be, a full-fledged general hospital or hospital section, which differs from the general hospital for acute illness only in the type of patients for whom it cares and the length of their hospitalization.

A "custodial" person is one whose needs are primarily in the areas of nursing care, infrequent medical supervision, or often only domiciliary care. Depending upon their individual requirements, such people should be placed in various institutions other than hospitals. Those who are in need of constant nursing care and only infrequent medical supervision may best be kept in separate buildings or wings connected with or adjoining general hospitals, since their conditions are such that immediate medical care may be at any time demanded. Placement of such people in adequately equipped private and voluntary nursing and old age homes is also a satisfactory solution. In 1954 the National Conference on the Long-Term Patient recommended a flexible arrangement with periodic re-evaluation of long-term patients to facilitate their placement in the most suitable environment, and their return to the community if improvement reaches a satisfactory level. This would not only allow these people to live in a more appropriate nonhospital facility, but would also give them the assurance of immediate medical assistance in case of emergency.

Another important step toward improvement would be revision of our present concept of hospital building programs, keeping in mind the gradual increase of aged and chronically ill persons. In building and organizing new institutions, the ever-increasing role of medical rehabilitation can no longer be disregarded. A wider use of rehabilitation, the restorative aspect of chronic medicine, would materially reduce the number of disabled people who now constitute a sizable proportion of the "custodials" in the public hospitals.

A major task in correcting this situation is to overcome the almost total disinterest of the medical profession in chronic diseases—a situation identified by Ginzberg[2] as "traditional negativism of most physicians in dealing with patients with long-term illness." In addition to the physiologic, pathologic, and clinical aspects of chronic diseases, the medical and allied professions will have to learn problems of the chronically ill patient, his place in society, and conversely the society's attitude toward him. Problems which are seemingly insignificant in the domain of acute illnesses, gain an ever-growing importance when the disease becomes chronic. The chronically ill patient is not merely a malfunctioning mechanism, but a human being who, in addition to his actual physical illness, suffers from a number of troubles often not immediately recognizable, and often

not even strictly medical. Without some solution of such issues, even the most skillful medical management will not result in complete restoration of the patient.

Indeed, this is how many patients become custodial: they go to the hospital for some acute or chronic disease and their physical health is improved or restored; but, their emotional and social problems unsolved, they remain in the hospital.[3]

These are only a few facets of this complex situation. The solution of one or some of them will not of necessity correct the issue of overhospitalization, which is the result of long years of procrastination. The attack will have to come simultaneously from several directions. Clinical, institutional, educational, and fundamental research must be intensified and, even more important, coordinated.

The curricula of medical, nursing, and other professional schools concerned with the care and management of the chronically ill patient must be thoroughly rearranged. The best research program, no matter how extensive and fundamental, will not provide the knowledge that the young physician needs when he faces the actual demands of everyday practice. Many medical schools have already recognized some of the obvious weaknesses in their curricula and have introduced appropriate changes. The problem, however, is too deep and old to be solved by minor changes in teaching schedules. It is a question of reorientation of the entire philosophy of medical education in the direction of a more comprehensive approach to everyday clinical questions.[4] All patients, but particularly the chronically ill, have clinical troubles which may be complicated and are often modified by emotional, social, economic, and other factors. These nonmedical complications can reach the point where the best conventional medical efforts will fail unless other personal factors are considered. The young graduate of our medical schools is insufficiently equipped to meet such complex issues. Unfamiliar with the depth and extent of the personal difficulties of his chronically ill patient, his best efforts are doomed to fail. The most common reaction to such repeated failures is a complete loss of interest in chronic illness. Little does the young doctor know that neither the apparent hopelessness of the disease nor a lack of his talent were responsible for failure. The responsibility rests on the shoulders of those who failed to alert him to the management of his patient as an integrated whole, and to equip him with the skills to accomplish this, or the patience to use them.

This discussion may not seem at first to have much bearing on our immediate problem—that is, the undue accumulation of "custodials" in public hospitals. It does not, however, require too elaborate thought to realize that the improperly managed chronically ill patient will often become "custodial." An informed practicing clinician, regardless of his specialty, can detect problems in his patient that would sooner or later lead to complications. An early elimination of often seemingly minor difficulties could prevent many people from undergoing the indignity of later custodial care.

The proper care of the chronically ill and even more so, that of the "custodial," is closely related to the general economic picture. It is in the field of the chronic diseases where the early impacts of an economic recession can be felt. This is partly due to the fact that most of these diseases require more prolonged medical

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and hospital care than a family with reduced income can afford. The adverse situation created by a chronic disease is further aggravated if it results in temporary or permanent disability. Low- or even middle-income families can rarely assume responsibility for the care of handicapped old people. Though such people may not need hospital care, they are left in institutions purely as a matter of exigency in the absence of other places to go. This is a good example of how illness aggravated by social and economic difficulties may lead to unnecessary and unjustifiably prolonged hospitalization. A well-oriented medical profession and a reorganized hospital and custodial program could do a great deal to eliminate the costly and unhappy presence of "custodials" from the public hospitals. Such corrective measures should be introduced while the general economic picture is favorable. In times of economic recessions only temporary and improvised measures can be instituted. Important as is the issue of the misplaced "custodial," it can and should be considered only as one significant aspect of the complex management of the chronically ill. It can be remedied by intelligent and mutual collaboration between all professional personnel concerned and the citizens of the community. A piecemeal solution of certain medical, emotional, public health, and social problems may result in temporary relief, but the increasing number of aged and many other factors will inevitably lead to further increase in the number of chronically ill and "custodials."

The evaluation of the medical necessities of the chronically ill and their separation from purely custodial care in a public institution involves interdisciplinary cooperation, medical, social, vocational, and administrative. The outlined approach here has been made from the clinician's point of view. Other disciplines approaching these issues from different tangents would surely have not only pertinent questions but definite ideas for solution. It is hoped that this statement of concept and philosophy will lead to further provocative discussions.

REFERENCES

1. Dacso, M. M., Novey, J., Kristeller, E. L., and Rusk, H. A.: Survey of Ninety-five Custodial Patients in a Municipal Hospital, Rehabilitation Monograph VII, 1954.
2. Ginzberg, E.: Pattern for Hospital Care, New York, 1950, Columbia University Press.
3. Roberts, D. W.: The Over-all Picture of Long-Term Illness, J. CHRON. DIS. **1**:149, 1955.
4. Berry, G. P.: Medical Education in Transition, J. Med. Education **28**:98, 1953.

MICHAEL M. DACSO, M.D., and
HOWARD A. RUSK, M.D.
Department of Physical Medicine and Rehabilitation
New York University College of Medicine
New York, N. Y.

Book Reviews

MORBIDITY IN THE MUNICIPAL HOSPITALS OF THE CITY OF NEW YORK. By Marta Fraenkel, M.D., and Carl L. Erhardt. Pp. 229; indexed. New York, 1955, Russell Sage Foundation. Price $4.50.

Illness in hospitals is an important component of all illness, especially when mental illness is included. Data on illness are undoubtedly recorded better and more systematically for hospitalized patients than for persons ill elsewhere, at least with respect to diagnosis. Little use of these data has been made except for clinical research.

This book is a report on an exploratory study of the 122,000 patients discharged from 31 of the 35 municipal hospitals in New York City during the six months ending October, 1952. The purpose of the study was to supply data needed in community planning for medical services. The municipal hospitals included are 14 general, 7 tuberculosis, 3 cancer, 2 psychiatric, 1 general chronic disease, and 4 communicable disease hospitals. Three voluntary hospitals also participated, although their data are not included in the report. The study was viewed by the agencies conducting it—the city departments of hospitals and of health—as an exploration of methodology and feasibility of a continuing hospital morbidity reporting system for all hospitals in the community, a system which is presently being put into effect.

The data presented on discharged patients include diagnosis, age, sex, race, length of stay, and condition on discharge. More detailed analyses are made of patients with obstetric, traumatic, and psychiatric conditions, tuberculosis, cancer, and "circulatory and other chronic diseases," and of child patients and aged patients.

The data show widely divergent lengths of stay for patients with nearly all diagnoses. Many patients with typically chronic diseases stayed for short periods, even excluding those dead at discharge. The fact that some patients were discharged with a diagnosis, e.g., of "delivery without complication" after a stay of 60 days may be due to a single "main diagnosis" having been selected. The main diagnosis is defined as "the final diagnostic statement of the condition for which the patient was admitted to the hospital." Other conditions, however, may have affected length of stay.

As the report clearly indicates, a hospital morbidity reporting system would be most useful for community planning for health services if it covers voluntary as well as governmental hospitals. The patients of municipal hospitals in New York City include disproportionate numbers of indigent and medically indigent, nonwhites, chronically ill, and aged persons.

Dean W. Roberts

PRACTICAL MEDICAL MYCOLOGY. By Edmund L. Keeney, M.D. Pp 145; indexed. Springfield, Ill., 1955, Charles C Thomas, Publisher. Price $4.50.

This very compact monograph on medical mycology is beamed directly to the practicing physician. The content is carefully selected to cover broadly the relative importance of the individual mycoses, the description of the responsible fungi, their epidemiology, clinical features, diagnostic measures, and, very strongly emphasized, treatment. Each of the mycoses is covered briefly in from three to ten pages (dermatophytosis appropriately tops with sixteen pages). Thirteen of the most important mycoses, plus the allergic fungus spores and fungi poisonous by ingestion, are presented. The text is readable, stripped down to easily-coped-with mycologic terms. Preceding all but a few of the sections of the minor mycoses are excellent diagrammatic illustrations of the essentials covered in the text. The references will enable an interested physician to probe more deeply in any area he may wish.

Keeney has a "feel" for phases all of us wish emphasized, such as the fact that mere recovery of *Candida albicans* is not adequate evidence for a diagnosis of moniliasis. Rarely, indeed, should the diagnosis of aspergillosis be made.

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No doubt most of those especially interested in a specific mycosis will have one or two points they would raise. This derives mainly from the compelling need for brevity, although admittedly the chart for the geographic distribution of coccidioidomycosis goes too far north. As one with understandable bias in coccidioidomycosis, I would indicate a place or two where amplification would have made this section even more outstanding. The statement that highest rate of dissemination is in pregnant women is theoretical and not proved. One would wish for a paragraph on coccidioidal pulmonary *cavities*, for, in the condensation, cavities are linked with the progressive infection, which association is exceedingly rare. As one of those clinging to the "old dogma" of noncontagion, I wonder what better basis there could be for this belief than "the fact that there is no man to man transmission of the disease." But truly, the discussion of coccidioidomycosis is admirable, reflecting Keeney's extensive personal experience in the laboratory and in practice.

This combination of experience in research and on the firing line of practice accounts for Keeney's notable success in his monograph. It is what the busy practitioner, resident, or medical student needs for a good overview which he can read in a few hours and then go back to for quick reference. He may then wish to follow up in a heavier round with a more detailed text or with references, but this is his everyday friendly guide.

Charles E. Smith

REHABILITATION MONOGRAPH I: AN EVALUATION OF REHABILITATION—A STUDY OF 476 CASES, WITH A DETAILED FOLLOW-UP STUDY OF 208 CASES DISCHARGED IN 1949 FROM THE PHYSICAL MEDICINE AND REHABILITATION SERVICES OF THE NEW YORK UNIVERSITY-BELLEVUE MEDICAL CENTER. By Georgia F. McCoy, M.S., and Howard A. Rusk, M.D. Pp. 87. New York, 1953, The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center. Price $1.00.

REHABILITATION MONOGRAPH II: PSYCHIATRIC ASPECTS OF REHABILITATION. By Morris Grayson, M.D., in collaboration with Anne Powers, M.S., and Joseph Levi, PH.D. Pp. 86. New York, 1952, The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center. Price $1.00.

REHABILITATION MONOGRAPH III: A BLADDER AND BOWEL TRAINING PROGRAM FOR PATIENTS WITH SPINAL CORD DISEASE. By Edith Buchwald, M.A., A.R.P.T., Margaret McCormack, R.N., and Emilie Raby, R.N. Pp. 35. New York, 1952, The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center. Price $1.00.

REHABILITATION MONOGRAPH IV: MANUAL OF PROCEDURES OF THE CHILDREN'S DIVISION INCLUDING OBJECTIVES, PHILOSOPHY, POLICIES AND STAFF FUNCTIONS OF THE CHILDREN'S DIVISION OF THE INSTITUTE OF PHYSICAL MEDICINE AND REHABILITATION, NEW YORK UNIVERSITY-BELLEVUE MEDICAL CENTER. By George G. Deaver, M.D., and Staff, in collaboration with the Association for the Aid of Crippled Children, New York City. Pp. 43. New York, 1952, The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center. Price $1.00.

REHABILITATION MONOGRAPH V: BRACES — CRUTCHES — WHEELCHAIRS: MODE OF MANAGEMENT. By George G. Deaver, M.D., and Anthony L. Brittis, M.D. Pp. 60. New York, 1953, The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center. Price $1.00.

REHABILITATION MONOGRAPH VI: SELF-HELP DEVICES FOR THE ARTHRITIC. By Edward W. Lowman, M.D. Pp. 123. New York, 1954, The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center. Price $1.00.

REHABILITATION MONOGRAPH VII: SURVEY OF NINETY-FIVE CUSTODIAL PATIENTS IN A MUNICIPAL HOSPITAL. By Michael M. Dacso, M.D., Joseph

Novey, M.S.W., and Edith L. Kristeller, M.D. Pp. 52. New York, 1954, The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center. Price $1.00.

REHABILITATION MONOGRAPH VIII: A MANUAL FOR TRAINING DISABLED HOMEMAKERS. By Howard A. Rusk, M.D., Edith L. Kristeller, M.D., Julia S. Judson, M.S., Gladys M. Hunt, R.N., and Muriel Zimmerman, O.T.R. New York, 1955, Pp. 167. The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center. Price $1.00.

REHABILITATION MONOGRAPH IX: CEREBRAL PALSY, METHODS OF EVALUATION AND TREATMENT. By George G. Deaver, M.D. Pp. 57. New York, 1955, The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center. Price $1.00.

A HOME PROGRAM FOR WHEEL CHAIR PATIENTS. By Edward E. Gordon, M.D. Pp. 19. The National Multiple Sclerosis Society, 270 Park Ave., New York, N. Y., 1952.

A HOME PROGRAM FOR THE CARE OF BED PATIENTS. By Edward E. Gordon, M.D. Pp. 14. The National Multiple Sclerosis Society, 270 Park Ave., New York, N. Y., 1952.

MULTIPLE SCLEROSIS. APPLICATION OF REHABILITATION TECHNIQUES. By Edward E. Gordon, M.D. Pp. 54. The National Multiple Sclerosis Society, 270 Park Ave., New York, N. Y., 1951.

A HOME PROGRAM FOR PATIENTS AMBULATORY WITH AIDS. By Edward E. Gordon, M.D. Pp. 19. The National Multiple Sclerosis Society, 270 Park Ave., New York, N. Y., 1952.

A HOME PROGRAM FOR INDEPENDENTLY AMBULATORY PATIENTS. By Edward E. Gordon, M.D. Pp. 16. The National Multiple Sclerosis Society, 270 Park Ave., New York, N. Y., 1952.

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Until recently a major energy expenditure of protagonists of rehabilitation was devoted toward efforts to assemble evidence for the worth-whileness of their services and for the argument that despite the considerable expense of rehabilitation, it was possible to suggest that tax-paying re-employed rehabilitated patients more than repaid for the services. The cogency of these arguments depended on the bias of the beholder. In fact, it is difficult to appraise rehabilitation. Patients with severe limitations are apt to be grateful for ordinarily trivial improvement and men of good will will agree that gains in morale for patients and their families and acquisitions in human dignity are beyond dollars and cents.

The series of monographs from The Institute of Physical Medicine and Rehabilitation and from the National Multiple Sclerosis Society are largely free from the defects of overenthusiasm which were a normal part of early efforts to overcome skepticism toward modern rehabilitation. Contents of each monograph are well indicated by the titles and the whole series may serve as an introduction to the field and as practical guides to the management of particular problems.

It remains true that the least satisfactory efforts lie in evaluation of rehabilitation. While some gains are easily assessed, for example, ambulation of a previously bed-ridden patient, other gains are subtler and their importance to the patients needs to be judged on the patient's own requirements rather than on an absolute scale. Buttoning a shirt may represent a major victory for one patient but an inconsequential one for another. Even if one accepts as a fact that the patient has gained a skill, it is difficult to assess the rehabilitation program. In the main, evaluation of rehabilitation has compared the results with the program to the results with no program. This is hardly fair since scarcely anyone since Plato has urged neglect of the patient no matter what may have been practiced. A program of any sort which offers hope must also stimulate the patient in ways which neglect is not apt to do. This fact produces a dilemma in design of a testing program. To what is a rehabilitation program to be compared? One does not deliberately

run a paired series of observations in which a full-scale rehabilitation program is matched with another one in which the wrong skills are taught. The question remains: granted that the full-scale rehabilitation program is worth while, how far can it be scaled down so that it may serve large numbers of people and still be effective?

Other monographs in The Institute series emphasize the care and patience required for specific problems and provide a step-by-step guide to training. The devices used are frequently ingenious and a tribute to the combined efforts of the rehabilitation team and the patients. In many cases they will serve to suggest other devices that can be rigged up to meet individual needs.

The National Multiple Sclerosis Society has similarly performed a great service. Although Dr. Gordon, who has written the full series of five monographs, aimed particularly at the care of patients with multiple sclerosis, the material is more generally applicable. These are immensely practical guides full of common sense and specific descriptions of techniques which may be useful wherever there are problems of spasticity, weakness, contractures, or incoordination.

Kenneth L. Zierler

SUMMARY OF SURVEY OF PHILANTHROPIC FOUNDATIONS. Excerpted from AMERICAN FOUNDATIONS AND THEIR FIELDS. By Wilmer Shields Rich. Ed. 7 Pp. 32. American Foundations Information Service. New York, N. Y., 1955. Sponsored by Raymond Rich Associates and Marts and Lundy, Inc.

Descriptions of 269 philanthropic foundations interested in health and medicine are included in the seventh edition of "American Foundations and Their Field," published this month by American Foundations Information Service, New York. Also indexed are descriptions of 159 foundations specifically interested in the physically handicapped, 378 in hospitals, 63 in medical care, 85 in medical education, 170 in medical research, 69 in mental health, and 60 in nursing.

In all, 4,162 foundations are described in the 784-page volume prepared by Mrs. Wilmer Shields Rich, director of the service. Most of these foundations are potential supporters of this specific field in view of their broad legal purposes. Indexing of fields of interest is predicated on specific mention of a field in a foundation's purpose, a foundation report of current interest in that field, or a record of a grant of $1,000 or more to an organization classifiable in that field.

The new edition results from the most comprehensive nationwide survey and analysis of foundations ever undertaken. Descriptions are based on data furnished by foundations themselves as well as on public records. In collecting information throughout the country, 25,000 photographs were made of portions of latest available tax returns and various legal documents.

Findings of the survey reveal that foundations in this country hold assets of more than $4,700,000,000 and make annual grants totalling more than $308,000,000. The foundations described are those which meet the generally accepted definition: a non-profit legal entity established to serve the welfare of mankind, having a principal fund of its own or receiving the charitable contributions of a living founder or founders, and governed by its own trustees or directors.

There are probably 7,300 foundations of this character in the country today, the author estimates. Even the Federal Government, however, does not know the exact number of foundations now in existence, their location, resources, legal structure or nature of activities. This is true because trustees are not required to file a return with the Internal Revenue Service until after a foundation has been in operation for 12 months.

Other principal findings are:

1. The bulk of resources is in the hands of relatively few foundations.

   A total of $4,200,000,000 or 93 per cent of all foundation assets, is held by fewer than 20 per cent of the foundations studied. The other 80 per cent have total assets of $298,798,000, less than the assets of either the Ford Foundation or The Rockefeller Foundation. A total of more than $1,500,000,000 is held by the seven largest foundations: The Ford Foundation, $493,213,842; The Rockefeller Foundation, $447,686,573; Carnegie Corporation of New York, $178,861,599; W. K. Kellogg Foundation, $109,812,214; The Duke Endowment, $109,552,000; The Commonwealth Fund, $105,993,035, and The Pew Memorial Foundation, $104,987,129.
2. Resources are concentrated in the wealthiest areas of the country.

Approximately 30 per cent of the foundations in the entire United States are situated in New York State, and 91 per cent of these are in New York City. Of the total reported assets, New York State has $2,500,000,000 or 55 per cent, with 98 per cent of this amount in New York City.

3. There is a definite relationship between size and pattern of operation.

Larger foundations—those with assets amounting to $1,000,000 or more or whose annual grants exceed $50,000—tend to concentrate in some chosen area, either advancing selected fields of work by supporting research, demonstrations and experiments, or utilizing funds to strengthen selected institutions, communities or regions. Small foundations give more like individuals, supporting causes with which they are familiar or which make effective appeals to them.

4. More than half of the foundations covered in the survey were established during the past fifteen years.

Only ten of these foundations were created prior to 1900, and only 270 existed in 1930. These were established in the main by millionaire philanthropists. The development of smaller foundations to serve as receptacles for tax savings began in the 1930's and reached an unexpected height in the 1940's. Of the foundations established between 1900 and 1929, only 44 per cent were in the "small" category, while 85 per cent of the foundations established in the 1940's were in this category. Since 1950, foundations have been set up at a rate of about 200 a year, with 82 per cent of them in the "small" category.

5. Both large and small foundations play important roles in philanthropy today.

"Although the grants of the small foundations may be dwarfed in size by the dramatic gifts of the largest foundations, they fill an indispensable niche in the budgets of charitable, educational, religious and scientific institutions," Mrs. Rich comments. "Their annual gifts to operating budgets often make it possible to put into practice the results of the research and experimentation financed by the largest foundations. Similarly, their undesignated gifts often make it possible to maintain the expanded facilities provided through larger gifts."

6. While social welfare is the prevailing concern of most foundations, support of institutions of higher education, including fellowships and scholarships, probably claims the largest amount of foundation gifts.

Foundations of all sizes show "a consuming interest in finding able individuals and helping them to develop their talents to the full, to the end of equipping them for leadership of society," the study concludes.

American Foundations Information Service, established in 1952 as the national center for foundation information, grew out of the foundation work conducted since 1939 by Raymond Rich Associates. Publication of the new edition of "American Foundations and Their Fields" was sponsored jointly by Raymond Rich Associates and Marts and Lundy, Inc., New York firms specializing in counsel to philanthropic organizations.

The first of this series of surveys was made in 1931 by the Twentieth Century Fund as a guide to its own planning. It showed economics to be the field least cultivated at that time, and largely influenced the Fund to concentrate its interest there.

The Fund published three editions of "American Foundations and Their Fields" between 1931 and 1935. Raymond Rich Associates then received the Fund's files and published editions in 1939, 1942 and 1948. The 1939 edition covered 243 foundations as contrasted to 4,162 described in the seventh edition.

In the foreword to the new edition, Evans Clark, trustee and former executive director of the Twentieth Century Fund, describes these volumes as "invaluable not only to those who give but also to those who seek to receive."

"Prior to their publication, there was no single source to which applicants for philanthropic aid could go for information as to the agencies most likely to be interested—judged by their past disbursements, their stated purposes, and their reported current fields of interest," he says, adding that the existence of this information also serves foundations by decreasing the number of applications for assistance entirely outside their chosen fields.

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